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OBSTETRICS

Increase in preterm stillbirths in association with reduction in iatrogenic preterm births during COVID-19 lockdown in Australia: a multicenter cohort study



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BACKGROUND: The COVID-19 pandemic has been associated with a worsening of perinatal outcomes in many regions around the world. Melbourne, Australia, had one of the longest and most stringent lockdowns worldwide in 2020 while recording only rare instances of COVID-19 infection in pregnant women.

OBJECTIVE: This study aimed to compare the stillbirth and preterm birth rates in women who were exposed or unexposed to lockdown restrictions during pregnancy.

STUDY DESIGN: This was a retrospective, multicenter cohort study of perinatal outcomes in Melbourne before and during the COVID-19 lockdown. The lockdown period was defined as the period from March 23, 2020 to March 14, 2021. Routinely-collected maternity data on singleton pregnancies ≥ 24 weeks gestation without congenital anomalies were obtained from all the 12 public hospitals in Melbourne. We defined the lockdown-exposed cohort as those women for whom weeks 20 to 40 of gestation occurred during the lockdown and the unexposed control group as women from the corresponding calendar periods 12 and 24 months before. The main outcome measures were stillbirth, preterm birth, fetal growth restriction (birthweight $<$ third centile), and iatrogenic preterm birth for fetal compromise. We performed multivariable logistic regression analysis to compare the odds of stillbirth, preterm birth, fetal growth restriction, and iatrogenic preterm birth for fetal compromise, adjusting for multiple covariates.

RESULTS: There were 24,817 births in the exposed group and 50,017 births in the control group. There was a significantly higher risk of preterm stillbirth in the exposed group than the control group (0.26% vs 0.18%;

adjusted odds ratio, 1.49; 95% confidence interval, 1.08–2.05; $P=.015$). There was also a significant reduction in the preterm birth of live infants < 37 weeks (5.68% vs 6.07%; adjusted odds ratio, 0.93; 95% confidence interval, 0.87–0.99; $P=.02$), which was largely mediated by a significant reduction in iatrogenic preterm birth (3.01% vs 3.27%; adjusted odds ratio, 0.91; 95% confidence interval, 0.83–0.99; $P=.03$), including iatrogenic preterm birth for fetal compromise (1.25% vs 1.51%; adjusted odds ratio, 0.82; 95% confidence interval, 0.71–0.93; $P=.003$). There were also significant reductions in special care nursery admissions during lockdown (11.53% vs 12.51%; adjusted odds ratio, 0.90; 95% confidence interval, 0.86–0.95; $P<.0001$). There was a trend to fewer spontaneous preterm births < 37 weeks in the exposed group of a similar magnitude to that reported in other countries (2.69% vs 2.82%; adjusted odds ratio, 0.95; 95% confidence interval, 0.87–1.05; $P=.32$).

CONCLUSION: Lockdown restrictions in Melbourne, Australia were associated with a significant reduction in iatrogenic preterm birth for fetal compromise and a significant increase in preterm stillbirths. This raises concerns that pandemic conditions in 2020 may have led to a failure to identify and appropriately care for pregnant women at an increased risk of antepartum stillbirth. Further research is required to understand the relationship between these 2 findings and to inform our ongoing responses to the pandemic.

Key words: cohort studies, COVID-19, pregnancy outcome, premature birth, stillbirth

Introduction

The COVID-19 pandemic has disrupted the delivery of maternity care globally, with a recent systematic review concluding that maternal and fetal outcomes had significantly worsened during the COVID-19 pandemic.¹ Some studies

have reported increases in stillbirth and reductions in preterm birth (PTB),^{2–8} whereas others reported no changes.^{9–13} These differences are likely because of multiple factors, including differences in study methodology,¹⁴ resource setting, severity of lockdown restrictions, and COVID-19 caseload.¹

The city of Melbourne, Australia, which has approximately 4000 births per month, experienced a prolonged period of lockdown restrictions commencing on March 23, 2020 through to March 14, 2021 (Figure 1). The strictest period of lockdown in mid-2020 restricted leaving the house for reasons other than approved essential work, caring for dependents, obtaining medical care or

essential food and services. Individuals were allowed 1 hour outside the home for exercise per day within a 5 km radius with a prohibition on all gatherings of > 2 people and a curfew from 8 PM to 5 AM.¹⁵

Numerous modifications to pregnancy care were concurrently adopted to mitigate the anticipated strain on health services and reduce infection risks. These measures included rapid transition to telehealth,¹⁶ hospital visitor restrictions, increasing the interval between in-person visits, reducing face-to-face appointment time, changes to gestational diabetes screening, and ultrasound surveillance of fetal growth.¹⁷ Melbourne experienced relatively few

Cite this article as: Hui L, Marzan MB, Potenza S, et al. Increase in preterm stillbirths in association with reduction in iatrogenic preterm births during COVID-19 lockdown in Australia: a multicenter cohort study. *Am J Obstet Gynecol* 2022;227:491.e1-17.

0002-9378/\$36.00

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<https://doi.org/10.1016/j.ajog.2022.04.022>



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AJOG at a Glance

Why was this study conducted?

The COVID-19 pandemic has been associated with worsening of perinatal outcomes in many regions around the world. The Australian city of Melbourne is a unique case study for the association between pandemic restrictions and pregnancy outcomes because of the stringency and length of the lockdown, the lack of significant health system strain, and very low COVID-19 maternity caseload.

Key findings

Lockdown restrictions in Melbourne during 2020 were associated with a significant increase in preterm stillbirths and a significant reduction in iatrogenic preterm birth for fetal compromise.

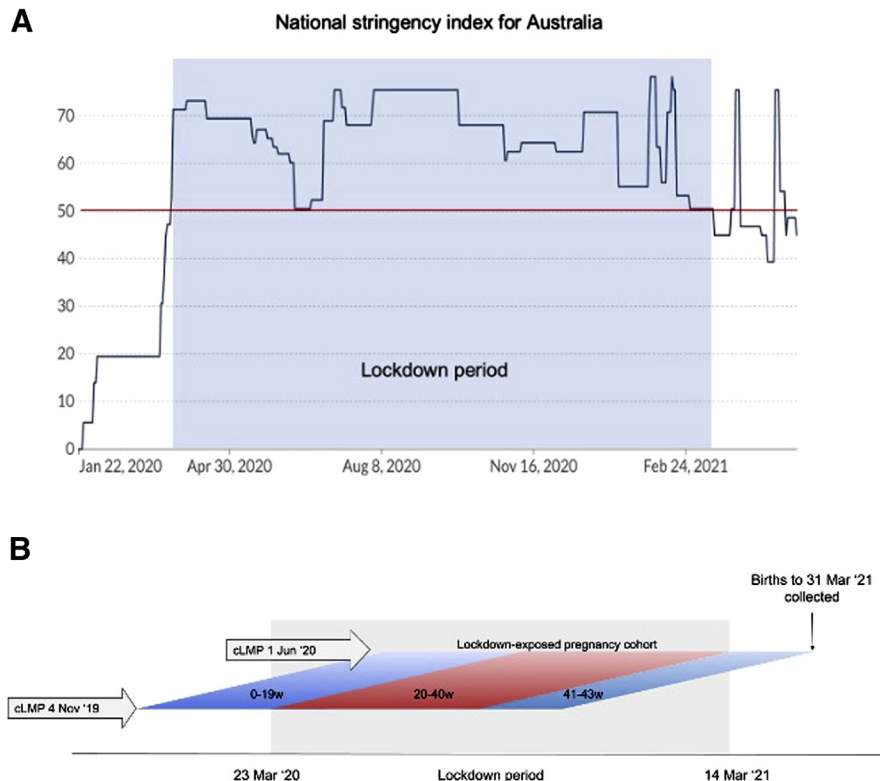
What does this add to what is known?

Pandemic restrictions in a high-income setting with a negligible maternal COVID-19 case load may have led to a failure to identify and appropriately care for pregnant women at an increased risk of antepartum stillbirth. These findings should inform the maternity sector's ongoing response to the COVID-19 pandemic.

maternal COVID-19 infections (<100 in 2020) and no associated maternal or perinatal deaths.¹⁸ This meant that metropolitan Melbourne experienced a unique set of circumstances not seen in other high-income countries: a prolonged period of significant social restrictions and major changes to antenatal care without an associated high burden of COVID-19 infections.

In mid-2020, all 12 Melbourne public maternity hospitals formed the Collaborative Maternity and Newborn Dashboard (CoMaND) for the COVID-19 pandemic project to internally monitor the effect of the pandemic on clinical quality indicators.¹⁹ Perinatal data collected for CoMaND were used here to analyse the impact of the lockdown on PTB, stillbirth, and utilization of maternity services.

FIGURE 1
National stringency index and cohort timeline



A, National stringency index for Australia by year/month from the Oxford Government Response Tracker. Blavatnik School of Government, University of Oxford. Available at: <https://www.bsg.ox.ac.uk/research/research-projects/covid-19-government-response-tracker>; **B**, Lockdown-exposed cohort timeline.

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Materials and Methods**Institutional review board approval**

This study was given ethical approval from the Human Research Ethics Committees of Austin Health (reference number HREC/64722/Austin-2020) and Mercy Health (reference number 2020-031).

Study population

We extracted routinely-collected data on births ≥ 24 weeks from all 12 public maternity hospitals in Melbourne from January 1, 2018 to March 31, 2021. Approximately three-quarters of all hospital births in Melbourne occur in these study sites. Births in exclusively private hospitals and planned home births outside of publicly-funded homebirth programs were not captured. However, women planning a private hospital or home birth would typically be transferred to a public hospital if they were at risk of PTB <31 weeks or required tertiary maternal-fetal medicine care.

Exclusions

Infants with congenital anomalies, terminations of pregnancy (TOP), non-Victorian residents, and multiple pregnancies were excluded. We excluded births <24 weeks gestation, as TOP can be provided on maternal request up to

this gestation, and management of PTB and preterm prelabor rupture of membranes < 24 weeks is variable and subject to parental discretion.

Definition of lockdown-exposed cohort and nonexposed controls

We defined the lockdown exposure period as March 23, 2020 to March 14, 2021, as this was a continuous period where the national stringency index (NSI) was ≥ 50 on the Oxford COVID-19 Government Response Tracker scale (Figure 1, B).²⁰ The NSI threshold of 50 was used in accordance with the definition of lockdown in the International Perinatal Outcomes in the Pandemic study.²¹

We used the calculated week of the last menstrual period rather than the week of birth to define the lockdown-exposed cohort to ensure that outcomes such as PTB would be measured using the denominator of births with a similar timing of lockdown exposure. We subtracted the infants' gestational age at birth in completed weeks from the week of birth to obtain the week of calculated last menstrual period (cLMP). Using this cLMP, we defined a "lockdown-exposed" cohort comprising women for whom weeks 20 to 40 of gestation would have occurred during the lockdown period. This included women whose cLMP occurred during the 31 weeks from November 4, 2019 to June 1, 2020, both dates inclusive (Figure 1, B). To control for possible seasonality, the control group comprised women who had their cLMP during the corresponding calendar weeks commencing 1 and 2 years before the start of the exposed cohort (births with cLMPs in weeks commencing November 5, 2018 to June 3, 2019 and November 6, 2017 to June 4, 2018). These were assessed as a combined control group.

Outcome measures

We calculated all the outcomes using both the denominators of "all births" (live and stillbirths) and "live births," with the exception of the stillbirth rate (calculated for "all births" only).

Primary outcomes

1. Total stillbirth rate stratified by gestational age
2. Total PTB (<37 weeks) rate

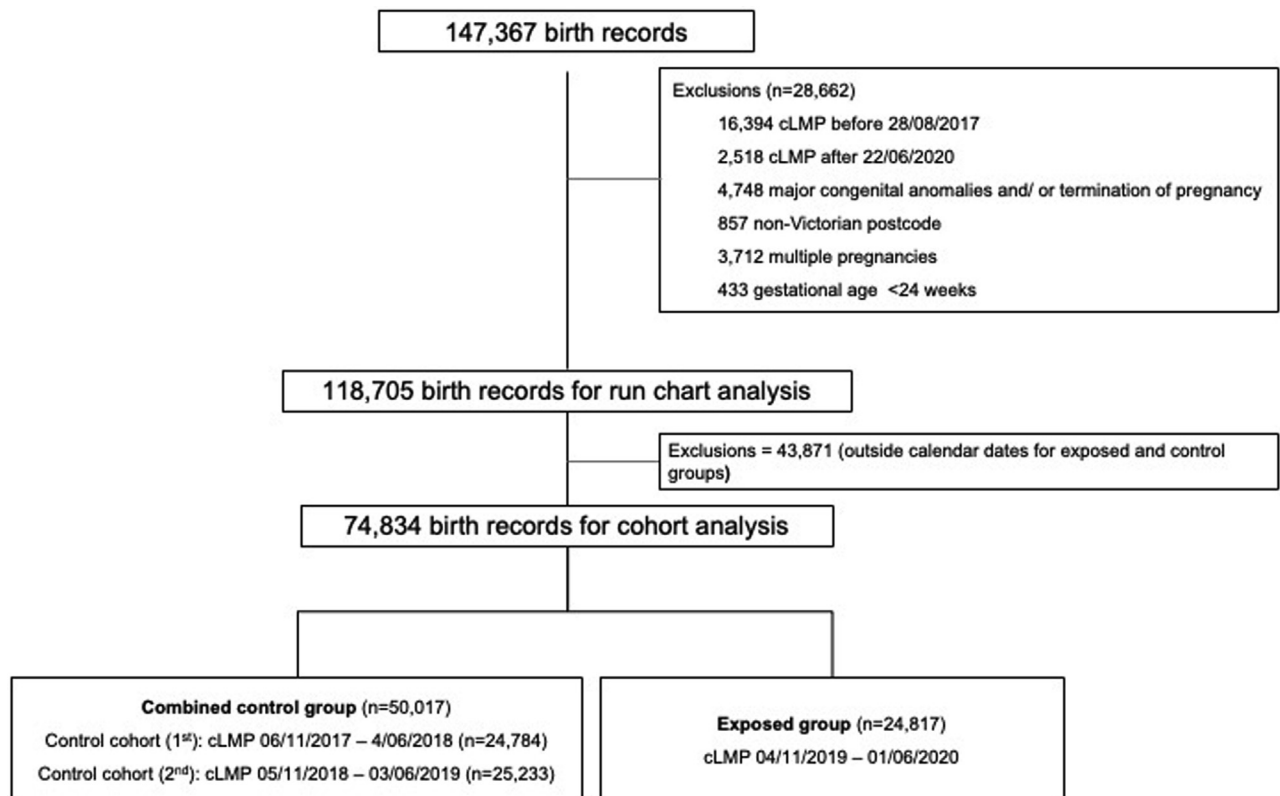
Secondary outcomes

1. PTB <37 weeks: spontaneous and iatrogenic. An iatrogenic birth was defined as any birth without spontaneous onset of labor (either induced labor or no labor).
2. PTB <32 weeks: total, iatrogenic, and spontaneous
3. PTB <28 weeks: total, iatrogenic, and spontaneous
4. Fetal growth restriction (FGR): total FGR, FGR at birth ≥ 37 weeks, <37 weeks, <32 weeks, and <28 weeks. FGR was defined as birthweight < third centile using local population sex-specific birthweight charts.²²
5. Iatrogenic births for fetal compromise: ≥ 37 weeks, <37 weeks, <32 weeks, and <28 weeks. Indications for induction of labor and cesarean delivery were coded according to the Australian Institute of Health and Welfare Metadata Online Registry, which defines fetal compromise as "suspected or actual fetal compromise and intrauterine growth restriction."²³ Any documentation of suspected fetal growth restriction, antepartum abnormal cardiotocography, "fetal distress" (without labor), reduced fetal movements, oligohydramnios, abnormal umbilical artery Doppler studies, or placental insufficiency were included in this classification.
6. Apgar score <7 at 5 minutes
7. Special care nursery (SCN) admission
8. Neonatal intensive care unit (NICU) admission
9. First antenatal visit ≤ 12 weeks gestation: this refers to the first planned visit to a midwife or doctor during pregnancy, whether community- or hospital-based.
10. Born before arrival (BBA): this refers to the rate of planned hospital births that occur before arrival, including unplanned births at home, in transit, or other locations.

Statistical analysis

No sample size calculation was performed, as this was a cohort defined by lockdown duration. Analyses of secondary outcomes were considered exploratory, and no adjustments for multiple comparisons were made. Perinatal outcomes were summarized as the proportion of all births (live births and stillbirths) and live births. Statistical significance was tested with the t-test or chi-squared test as appropriate. We performed multiple imputations by chained equation (MICE) to account for missing data from our dataset and created 5 imputed datasets (for statistical details see Supplemental file 1). We performed multivariable logistic regression analysis to obtain the adjusted odds ratio (OR) of the primary and secondary outcomes in the lockdown-exposed vs nonexposed cohorts. We adjusted for the following maternal covariates: maternal age, body mass index (BMI) at first antenatal visit, region of birth, need for interpreter (proxy indicator for primary language and categorized as yes or no), parity, socioeconomic status (assigned by maternal postcode), and smoking in pregnancy status. These covariates were chosen using subject matter knowledge. Statistical analyses were conducted using Stata 17 (release 17; StataCorp LLC, College Station, TX), and 2-sided *P* values below .05 were considered statistically significant. Because maternal BMI and smoking status were potentially on a causal pathway between lockdown restrictions and perinatal outcomes, we performed a sensitivity analysis without adjustment for these covariates.

We used Cox regression to derive the hazard ratios of stillbirths and PTB <37 weeks and Kaplan-Meier curves to plot the cumulative hazard of the outcomes of interest. We tested the proportionality of the hazards of control and exposed cohorts using Schoenfeld residuals. The ORs of the primary outcomes for each hospital were plotted in forest plots using meta-analysis of aggregated ORs per hospital. We used a fixed effect model to derive the pooled exponentiated effect measures (OR), because all the results are obtained on the same dataset, and the

FIGURE 2
Study flowchart

cLMP, calculated last menstrual period.

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heterogeneity across all outcomes was small for all outcomes except overall PTB, with $I^2 < 30\%$.

Births included in run chart analysis

To examine the temporal patterns in outcomes during lockdown conditions, we also generated run charts by week of cLMP. Run charts are a commonly-used method for detecting nonrandom safety signals in healthcare where an outcome measure is charted over time with probability-based rules for safety signals such as shifts and trends.²⁴ Only births with cLMP in the weeks from August 14, 2017 to June 22, 2020 were included in the run charts, comprising infants for whom weeks 20 to 43 of gestation occurred within the data collection period of January 1, 2018 to March 31, 2021. The prepandemic median rates for each outcome were calculated for the nonexposed cohort. A significant shift in

a run chart was defined as 6 or more consecutive weeks all above or below the prepandemic median according to the established definitions.²⁴

Results

There were 147,367 births in the participating hospitals during the period from January 1, 2018 to March 31, 2021. After all exclusions, there were 118,705 births remaining for the run chart analysis by week of cLMP (Figure 2).

Cohort analysis: lockdown-exposed vs nonexposed pregnancies

The lockdown-exposed cohort contained 24,817 births, and the control cohort contained a combined total of 50,017 births (Figure 2). The characteristics of exposed and control groups are shown in Table 1. The lockdown-exposed group differed significantly from the control group in terms of age,

socioeconomic class distribution, maternal region of birth, and maternity service level, though the absolute differences were small. Details of the bivariate analysis are available in Supplemental Table 1. The outcomes are presented using all birth denominators (live and stillbirths) in Table 2 and live birth denominators in Table 3. The results all remained robust in the sensitivity analysis excluding covariates of smoking and BMI.

Primary outcomes Stillbirths

There was a significantly higher rate of stillbirth in the lockdown-exposed group than the control group (0.34% vs 0.25%; adjusted odds ratio [aOR], 1.37; 95% confidence interval [CI], 1.04–1.81; $P=.03$) (Table 2). When stratified by gestational age, only preterm stillbirths <37 weeks remained significantly increased in the exposed

TABLE 1
Maternal characteristics among control and exposed cohorts (all births)

| Maternal characteristics | Exposed (n=24,817) | Control (n=50,017) | Pvalue |
|--------------------------------------|-----------------------|-----------------------|--------|
| Maternal age, mean (SD) | 31.9 (4.87) | 31.7 (4.95) | <.001 |
| Weight in kg, mean (SD) | 70.39 (17.13) | 70.20 (17.28) | .17 |
| Height in cm, mean (SD) | 163.17 (7.19) | 163.26 (7.05) | .14 |
| Smoking in pregnancy, n (%) | 1333 (5.37) | 2760 (5.52) | .41 |
| BMI categories, n (%) | | | |
| <18 | 311 (1.29) | 654 (1.33) | .14 |
| 18–24 | 11,535 (47.96) | 24,167 (48.90) | |
| 25–29 | 7085 (29.46) | 14,106 (28.54) | |
| 30–34 | 2976 (12.37) | 6128 (12.40) | |
| 35–39 | 1318 (5.48) | 2647 (5.36) | |
| ≥40 | 824 (3.43) | 1718 (3.48) | |
| Region of birth, n (%) | | | |
| Americas | 397 (1.61) | 744 (1.49) | <.001 |
| Australia and Associated Territories | 12,347 (50.05) | 24,433 (49.02) | |
| North Africa and Middle East | 1155 (4.68) | 2569 (5.15) | |
| Northeast Asia | 926 (3.75) | 2335 (4.68) | |
| Northwest Europe | 725 (2.94) | 1468 (2.95) | |
| Oceania including Antarctica | 955 (3.87) | 1913 (3.84) | |
| Southeast Asia | 2100 (8.51) | 4370 (8.77) | |
| Southern and Central Asia | 4823 (19.55) | 9408 (18.87) | |
| Southern and Eastern Europe | 484 (1.96) | 1064 (2.13) | |
| Sub-Saharan Africa | 755 (3.06) | 1543 (3.10) | |
| Parity, n (%) | | | |
| 0 | 10,919 (44.00) | 21,963 (43.91) | .95 |
| 1 | 8893 (35.83) | 18,030 (36.05) | |
| 2 | 3222 (12.98) | 6449 (12.89) | |
| ≥3 | 1783 (7.18) | 3575 (7.15) | |
| SEIFA quintile, n (%) | | | |
| 1 - Most disadvantaged | 5512 (22.21) | 10,941 (21.87) | .0040 |
| 2 | 3575 (14.41) | 7396 (14.73) | |
| 3 | 6097 (24.57) | 11,940 (23.87) | |
| 4 | 5562 (22.41) | 11,070 (22.13) | |
| 5 - Most advantaged | 4071 (16.40) | 8697 (17.39) | |

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(continued)

group (0.26% vs 0.18%; aOR, 1.49; 95% CI, 1.08–2.05; $P = .015$) (Table 4). Most of the fetal deaths were diagnosed before the onset of labor (Table 4). The hazard curve showed a significant gap in the trajectories of lockdown-exposed and

control groups in terms of cumulative hazard of stillbirth by gestational age (Figure 3, A). Maternal characteristics in the exposed and control stillbirth groups are provided in Supplementary Table 2.

Total preterm birth <37 weeks

There was a trend to reduced total PTB <37 weeks for all births (5.93% vs 6.23%; aOR, 0.94; 95% CI, 0.88–1.00; $P = .06$) (Table 2) and a statistically significant reduction in PTB <37 weeks for live births only (5.68% vs 6.07%; aOR, 0.93; 95% CI, 0.87–0.99; $P = .02$) (Table 3). The hazard curve showed significant separation of the trajectories of lockdown-exposed and control groups from 33–36 weeks of gestational age (Figure 3, B). The forest plots of stillbirths and total PTB by hospital and maternity service capacity are shown in Figure 4.

Secondary outcomes

Preterm birth <37 weeks, iatrogenic and spontaneous; all births and live births

There was no significant reduction in iatrogenic PTB <37 weeks for all births (3.24 vs 3.42; aOR, 0.94; 95% CI, 0.86–1.02; $P = .13$) (Table 2), but there was a significant reduction in iatrogenic PTB for live births (3.01 vs 3.27%; aOR, 0.91; 95% CI, 0.83–0.99; $P = .03$) (Table 3). There was no significant difference between the exposed and control groups in the rates of spontaneous PTB < 37 weeks' gestation for all births (2.69% vs 2.82%; aOR, 0.95; 95% CI, 0.87–1.05; $P = .32$) or live births (2.68% vs 2.80; aOR, 0.95; 95% CI, 0.84–1.05; $P = .32$). Forest plots of iatrogenic and spontaneous PTB <37 weeks by hospital are provided in Supplementary Figure 1.

Preterm birth <32 weeks, preterm birth <28 weeks; total, iatrogenic, and spontaneous

There were consistent trends toward lower PTB at <32 and <28 weeks for all births and live births, including total, iatrogenic, and spontaneous PTB (Tables 2 and 3).

Iatrogenic births for fetal compromise (live births only)

There was a significant reduction in iatrogenic births for fetal compromise in the exposed group than the control group. This reduction was significant for gestational age groups ≥37, < 37, and <28 weeks (Table 5).

TABLE 1
Maternal characteristics among control and exposed cohorts (all births)
 (continued)

| Maternal characteristics | Exposed (n=24,817) | Control (n=50,017) | Pvalue |
|--------------------------------------|-----------------------|-----------------------|--------|
| Maternity service level ^a | | | |
| Level 4 | 7199 (29.05) | 14,578 (29.19) | |
| Level 5 | 4931 (19.90) | 10,256 (20.54) | .01 |
| Level 6 | 12,531 (50.57) | 24,926 (49.91) | |

BMI, body mass index; SD, standard deviation; SEIFA, socioeconomic index for areas.

^a Level 6 maternity services provide regional or statewide specialized care for high-risk pregnancies, including extremely preterm births, and local care for all women and babies; Level 5 services care for normal- to moderate-risk pregnancies and manage labor and birth from 31 weeks gestation; Level 4 services provide local care for women and babies at normal and moderate risk, including planned births from 34 weeks gestation.

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Fetal growth restriction

There was no significant difference between the exposed and control groups in the rate of FGR among all births. There was a higher prevalence of FGR among preterm infants in the exposed cohort, but this did not reach statistical significance for any of the gestational age subgroups (Supplemental Table 3).

Apgar score <7 at 5 minutes and admissions to special care nurse and neonatal intensive care unit (live births)

There was no significant difference in low Apgar scores between the live infants in the exposed and control groups

TABLE 2
Primary and secondary outcomes for all births (live births and stillbirths)

| Outcomes | Exposed (n=24,817) | Control (n=50,017) | aOR ^a | | | Pvalue |
|----------------------------------|-----------------------|-----------------------|------------------|------|------|--------|
| | | | aOR | L | U | |
| Stillbirths | | | | | | |
| Total | 85 (0.34) | 125 (0.25) | 1.37 | 1.04 | 1.81 | .03 |
| Preterm birth <37 wk | | | | | | |
| Total | 1471 (5.93) | 3117 (6.23) | 0.94 | 0.88 | 1.00 | .06 |
| Spontaneous | 667 (2.69) | 1408 (2.82) | 0.95 | 0.87 | 1.05 | .32 |
| Iatrogenic | 804 (3.24) | 1709 (3.42) | 0.94 | 0.86 | 1.02 | .13 |
| Preterm birth <32 wk | | | | | | |
| Total | 234 (0.94) | 476 (0.95) | 0.98 | 0.84 | 1.15 | .81 |
| Spontaneous | 98 (0.39) | 212 (0.42) | 0.93 | 0.73 | 1.18 | .54 |
| Iatrogenic | 136 (0.55) | 264 (0.53) | 1.03 | 0.83 | 1.26 | .81 |
| Preterm birth <28 wk | | | | | | |
| Total | 75 (0.30) | 154 (0.31) | 0.98 | 0.74 | 1.29 | .87 |
| Spontaneous | 34 (0.14) | 74 (0.15) | 0.93 | 0.62 | 1.39 | .72 |
| Iatrogenic | 41 (0.17) | 80 (0.16) | 1.03 | 0.70 | 1.50 | .89 |
| Newborn outcomes | | | | | | |
| Apgar score < 7 at 5 min | 354 (1.43) | 758 (1.58) | 0.97 | 0.87 | 1.09 | .63 |
| Fetal growth restriction | 493 (2.00) | 1010 (2.02) | 0.99 | 0.89 | 1.10 | .84 |
| SCN admission | 2851 (11.53) | 6242 (12.51) | 0.90 | 0.86 | 0.95 | <.0001 |
| NICU admission | 551 (2.23) | 1113 (2.23) | 0.99 | 0.89 | 1.10 | .88 |
| Pregnancy care indicators | | | | | | |
| First antenatal visit ≤12 wk | 18,474 (74.44) | 29,488 (58.96) | 2.04 | 1.98 | 2.12 | <.0001 |
| Born before arrival | 142 (0.57) | 248 (0.50) | 1.17 | 0.95 | 1.45 | .13 |

aOR, adjusted odds ratio; L, lower limit of 95% confidence interval; NICU, neonatal intensive care unit; SCN, special care nursery; U, upper limit of 95% confidence interval.

^a Adjusted for age group, socioeconomic indexes for areas, parity, BMI, smoking status, interpreter requirement, fetal sex. Logistic regression analysis used "multiple imputations by chained equation" (MICE) to account for missing data: infant sex=1 (<0.01%), fetal growth restriction=147(0.17%), maternal age=109 (0.13%), country of birth=320 (0.38%), and Apgar score=116 (0.14%).

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TABLE 3
Primary and secondary outcomes for live births

| Outcomes | Exposed (n=24,732) | Control (n=49,892) | aOR ^a | | | Pvalue |
|------------------------------|-----------------------|-----------------------|------------------|------|------|--------|
| | | | aOR | L | U | |
| Preterm birth <37 wk | | | | | | |
| Total | 1406 (5.68) | 3029 (6.07) | 0.93 | 0.87 | 0.99 | .02 |
| Spontaneous | 662 (2.68) | 1397 (2.80) | 0.95 | 0.87 | 1.05 | .32 |
| iatrogenic | 744 (3.01) | 1632 (3.27) | 0.91 | 0.83 | 0.99 | .03 |
| Preterm birth <32 wk | | | | | | |
| Total | 194 (0.78) | 422 (0.85) | 0.92 | 0.77 | 1.09 | .33 |
| Spontaneous | 94 (0.38) | 202 (0.40) | 0.93 | 0.73 | 1.19 | .58 |
| iatrogenic | 100 (0.40) | 220 (0.44) | 0.91 | 0.71 | 1.15 | .41 |
| Preterm birth <28 wk | | | | | | |
| Total | 51 (0.21) | 119 (0.24) | 0.87 | 0.62 | 1.20 | .39 |
| Spontaneous | 32 (0.13) | 67 (0.13) | 0.97 | 0.64 | 1.48 | .89 |
| iatrogenic | 19 (0.08) | 52 (0.10) | 0.74 | 0.44 | 1.25 | .26 |
| Newborn outcomes | | | | | | |
| Apgar score < 7 at 5 min | 354 (1.43) | 758 (1.58) | 0.97 | 0.87 | 1.09 | .63 |
| Fetal growth restriction | 493 (2.00) | 1010 (2.02) | 0.99 | 0.89 | 1.10 | .84 |
| SCN admission | 2851 (11.53) | 6242 (12.51) | 0.90 | 0.86 | 0.95 | <.001 |
| NICU admission | 551 (2.23) | 1113 (2.23) | 0.99 | 0.89 | 1.10 | .88 |
| Pregnancy care indicators | | | | | | |
| First antenatal visit ≤12 wk | 18,420 (74.48) | 29,415 (58.96) | 2.05 | 1.98 | 2.12 | <.001 |
| Born before arrival | 141 (0.57) | 247 (0.49) | 1.05 | 0.91 | 1.21 | .52 |

aOR, adjusted odds ratio; L, lower limit of 95% confidence interval; NICU, neonatal intensive care unit; SCN, special care nursery; U, upper limit of 95% confidence interval.

^a Adjusted for age group, socioeconomic indexes for areas, parity, body mass index, smoking status, interpreter requirement, fetal sex. Logistic regression analysis used "multiple imputations by chained equation" (MICE) to account for missing data: infant sex=1 (<0.01%), fetal growth restriction=147(0.17%), maternal age=109 (0.13%), country of birth=320 (0.38%), Apgar score=116 (0.14%).

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(Table 3). There was a significant reduction in admissions to the SCN in the exposed group (11.53% vs 12.51%; aOR, 0.90; 95% CI, 0.86–0.95; $P<.001$). There was no significant difference in admissions to the NICU.

Pregnancy care indicators (all births)

A significantly higher proportion of women in the exposed group had their first antenatal visit ≤12 weeks gestation compared with the unexposed group (74.44% vs 58.96%; aOR, 2.05; 95% CI, 1.98–2.12; $P<.001$) (Table 1). There was a nonsignificant trend to more infants BBA to hospital, from 0.50% to 0.57% (aOR, 1.05; 95% CI, 0.91–1.21; $P=.52$)

in the lockdown-exposed group (Table 3).

Run chart analysis

There was a median of 801 total births per week during the run chart analysis period. There was a significant downward shift in new pregnancies during March 2020 to April 2020 at the onset of lockdown, followed by a significant rebound above the median in May and June (Figure 5, A). Run charts of primary outcomes by week of cLMP confirmed the temporal relationship between lockdown restrictions and the significant changes observed in the cohort analysis. There was a significant shift to more stillbirths after the onset of lockdown

(Figure 5, B) and shifts to fewer PTBs <37 weeks (Figure 6, A). Run charts of the secondary outcomes were consistent with the cohort analysis, except for the outcome measure of the first antenatal visit ≤12 weeks (Figure 7). The run chart displaying the rates of the first antenatal visit ≤12 weeks demonstrated an upward secular trend that predated the lockdown (Figure 8, A).

Comment Principal findings

Our multicenter cohort study assessing the perinatal outcomes during lockdown in the absence of high COVID-19 disease rates demonstrated a significant increase in preterm stillbirths. FGR has the largest

TABLE 4
Stillbirths by timing and gestational age

| Stillbirth subgroups | Exposed (n=24,817) n, (%) | Control (n=50,017) n, (%) | aOR ^a | | | P value |
|--------------------------|---------------------------------|---------------------------------|------------------|------|------|------------|
| | | | aOR | L | U | |
| Timing of fetal death | | | | | | |
| Before labor | 76 (89.41) | 104 (83.20) | 1.47 | 1.1 | 1.98 | .010 |
| During labor | 2 (2.35) | 4 (3.20) | 0.98 | 0.18 | 5.36 | .98 |
| Unknown | 7 (8.24) | 17 (13.60) | 0.83 | 0.34 | 2.01 | .68 |
| Gestational age at birth | | | | | | |
| Total births | 85 (0.34) | 125 (0.25) | 1.37 | 1.04 | 1.81 | .026 |
| Term ≥37 wk | 20 (0.08) | 37 (0.07) | 1.10 | 0.64 | 1.89 | .74 |
| Preterm <37 wk | 65 (0.26) | 88 (0.18) | 1.49 | 1.08 | 2.05 | .015 |
| Preterm <32 wk | 40 (0.16) | 54 (0.11) | 1.49 | 0.99 | 2.24 | .058 |
| Preterm <28 wk | 24 (0.10) | 35 (0.07) | 1.37 | 0.82 | 2.31 | .23 |

aOR, adjusted odds ratio; L, lower limit of 95% confidence interval; U, upper limit of 95% confidence interval.

^a Adjusted for age group, socioeconomic indexes for areas, parity, smoking status, interpreter requirement, fetal sex. Body mass index not included as covariate because of multiple imputation errors (perfect predictions) and multicollinearity in logistic regression. Logistic regression analysis used "multiple imputations by chained equation" (MICE) to account for missing data: infant sex=1 (<0.01%), fetal growth restriction=147(0.17%), maternal age=109 (0.13%), country of birth=320 (0.38%), Apgar score=116 (0.14%).

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population-attributable risk for stillbirth, with a 5-fold higher stillbirth risk if FGR is undetected antenatally.²⁵ We found no difference in the overall prevalence of FGR between the exposed and control groups, suggesting that the rise in stillbirths was not because of an increase in the risk profile of our population.

In tandem with the rise in preterm stillbirths was a significant reduction in PTB of live infants, driven by significant reductions in iatrogenic PTB and iatrogenic PTB for fetal compromise. This reduction in iatrogenic PTB was consistent across all hospitals, including those caring for low-, medium-, and high-risk pregnancies, supporting our conclusion that this was a widespread effect of the lockdown and not institution-specific responses to the pandemic.

Results in the context of what is known

Our observed increases in stillbirth and reductions in the total PTBs are similar in magnitude to those reported for a subgroup of high-income countries in a meta-analysis by Chmielewska and colleagues, though neither of these outcomes met statistical significance in

that meta-analysis.¹ Our cohort is larger than 7 of the 8 individual studies included in that meta-analysis and therefore makes a substantial contribution to the published experience from high-income countries.

The lack of significant change in spontaneous PTB in our study contrasts with findings from 2 institution-based studies from the United States that did find a significant reduction in spontaneous PTB.^{11,26} This difference is likely influenced by different baseline rates of PTB, demographic profiles, and COVID-19 caseloads in the US. We await the results of the International Perinatal Outcomes in the Pandemic study (iPOP) for more insights into the relationship between perinatal outcomes during the pandemic, income settings, and between-country differences.²¹

Clinical implications

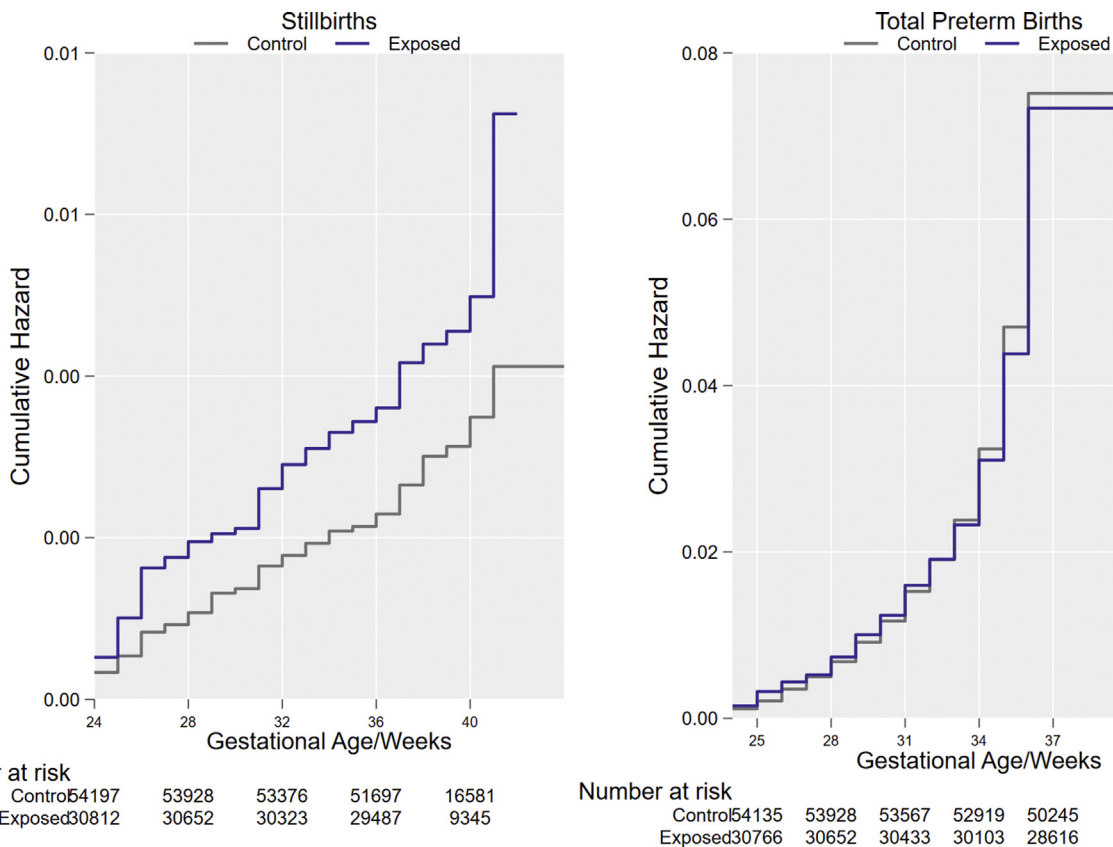
Taken together, the increase in preterm stillbirth and reduction in iatrogenic PTBs raises concerns that the maternity sector failed to maintain prepandemic standards of detection, surveillance, and timely delivery for high-risk pregnancies during the lockdown period. There was

no evidence that the number of at-risk fetuses increased, as the prevalence of severe FGR remained stable; also, there was no indication of a lack of engagement in antenatal care (as measured by gestation at first antenatal visit) or deficiencies in intrapartum care (as measured by Apgar score and intrapartum stillbirths). It is notable that the higher stillbirth rates and lower iatrogenic PTB rates were observed across most of the hospitals. It may be that a maternal reluctance to present to hospital for decreased fetal movements or other medical concerns may have contributed to these outcomes rather than institution-specific barriers to in-person care. The trend to more babies born before arrival to hospital during lockdown suggests that women were delaying presentation in labor, possibly because of fears about the risks of inpatient care, concerns regarding restrictive visiting policies for support persons in maternity wards, or home care responsibilities for other children.

Research implications

Pregnant women and maternity health-care workers in Melbourne experienced

FIGURE 3
Stillbirth and preterm birth hazard ratios



*Survival plots used the multiple imputed dataset

CI, confidence interval; HR, hazard ratio.

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increased stress and anxiety during 2020.²⁷ Further research is needed to understand whether the increase in preterm stillbirths is related to health service access, utilization, altered maternal pathophysiology, or other social and environmental factors. The reduction in iatrogenic PTB during COVID-19 may be because of higher threshold for medically-indicated PTB owing to resource constraints or a failure to identify high-risk pregnancies at risk of stillbirth. It is important to note that the alternative to lockdown restrictions (ie, “care as usual” during the pandemic) may have been associated with worse outcomes as a result of more maternal and hospital staff COVID-19 infections, as our study cohort was drawn from the pre-COVID-19 vaccine era.

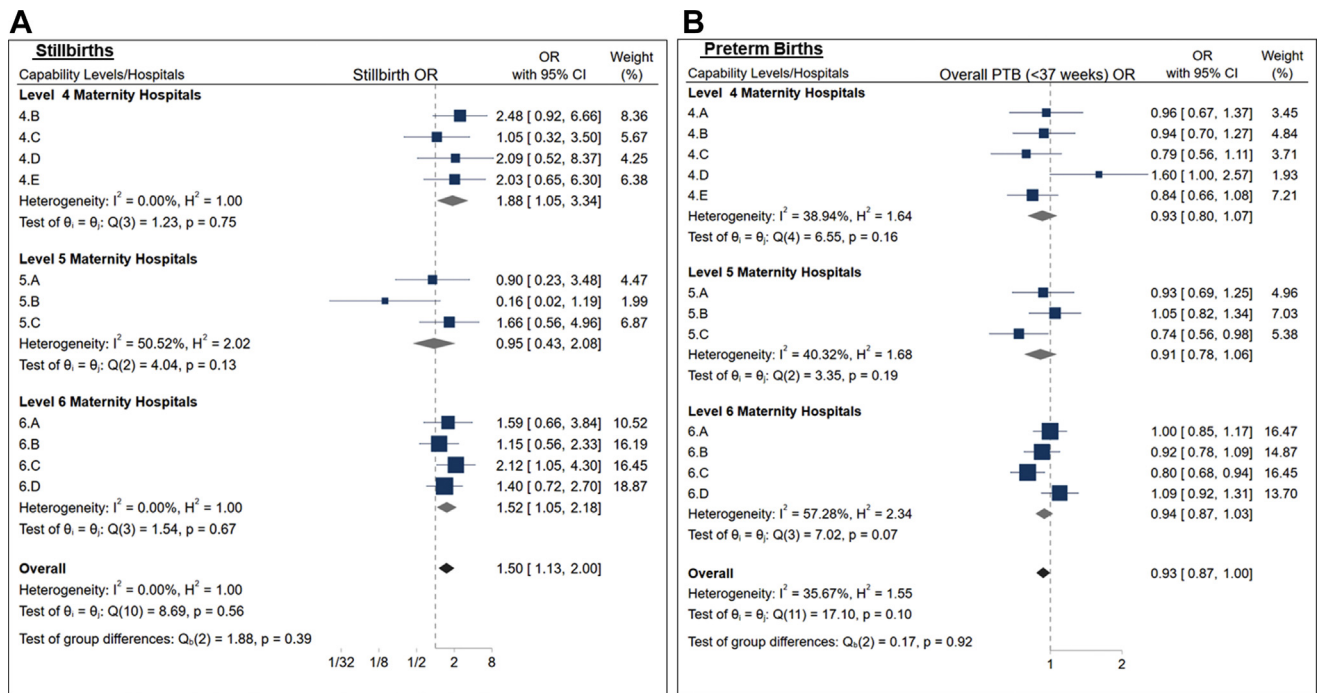
However, there were also some possible improvements in the perinatal outcomes during the lockdown. The trend to fewer spontaneous PTBs is consistent with reports from other high-income countries, though it is unclear what features of lockdown may have contributed to lower spontaneous PTB rates. It is also possible that there are net benefits to the reduction in iatrogenic PTB, including the clinically significant decline in SCN admissions, but this needs to be weighed against the possible association with increased stillbirths.

Strengths and limitations

Melbourne is a unique case study for the association between pandemic

restrictions and pregnancy outcomes because of the stringency and length of lockdown, the lack of significant health system strain, and very low COVID-19 maternity caseload (<100 total maternal infections during the study period with no associated maternal or perinatal deaths). In any study examining PTB during the pandemic, it is critical to have geographic coverage of all levels of maternity services, as patient presentation and interhospital transfer patterns may be altered. Our report has the strengths of a large sample size, detailed dataset, and complete outcome ascertainment of all public hospital births. Our adverse results can therefore be solely attributed to indirect effects of the pandemic.

FIGURE 4
Forest plots of primary outcomes by hospital and maternity service level



A, Odds ratio of stillbirth; B, Odds ratio of preterm birth <37 weeks.

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Our analysis also addresses the hidden perinatal mortality inherent in studies that report reductions in live PTBs without including stillbirths.²⁸ We heeded the recent call of the International Stillbirth Alliance to report both PTB and stillbirths, distinguish antepartum from intrapartum

stillbirths, and achieve an adequately-sized control group.²⁹ Furthermore, our study defined cohorts by cLMP rather than the date of birth to allow proper calculation of the outcome rates using women with similar timing of exposure to lockdown conditions and to avoid skewing the ascertainment of

preterm or term births at the beginning and end of the birth data collection periods.

The major limitation of our study is the omission of exclusively private hospital births, which make up about one-quarter of the total births in Melbourne. Private hospitals care for low- to moderate-risk women of higher socioeconomic status than public hospitals and have markedly different outcomes, including higher rates of term inductions of labor, higher number of cesarean deliveries, and higher rates of undetected FGR.³⁰ Our results are therefore not generalizable to perinatal outcomes in private hospitals.

Conclusions

Lockdown conditions are associated with significant changes in perinatal outcomes independent of the effect of the COVID-19 disease. Our study shows that pregnant women exposed to a

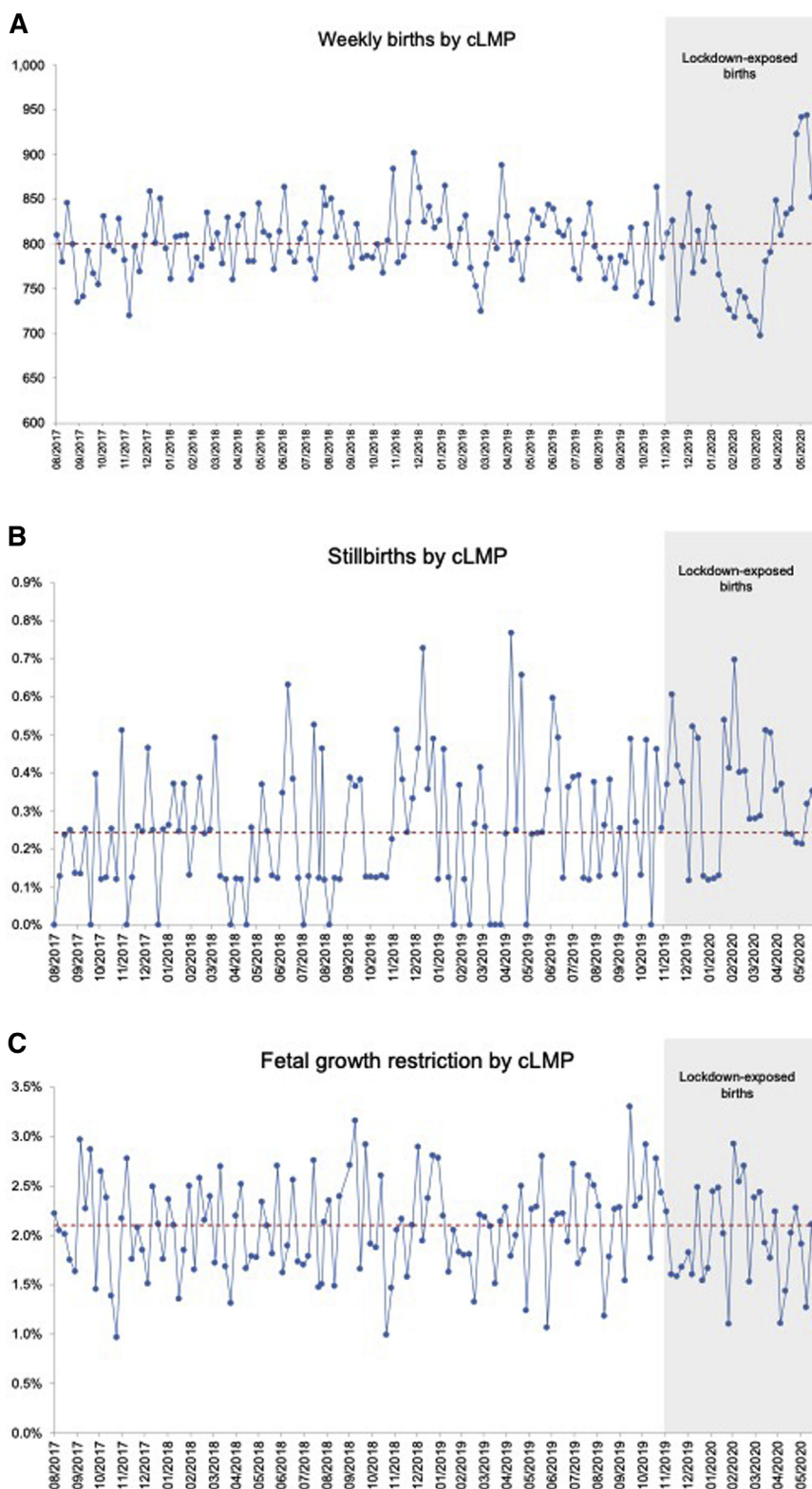
TABLE 5
Iatrogenic births for fetal compromise (live births only)

| Gestational age | Exposed (n=24,732) | Control (n=49,892) | aOR | | | |
|-----------------|--------------------|--------------------|------|------|------|--------|
| | | | aOR | L | U | |
| Total births | 4199 (16.98) | 9245 (18.53) | 0.89 | 0.85 | 0.93 | <.0001 |
| ≥37 wk | 3890 (15.73) | 8494 (17.02) | 0.90 | 0.87 | 0.94 | <.0001 |
| < 37 wk | 309 (1.25) | 751 (1.51) | 0.82 | 0.71 | 0.93 | .003 |
| < 32 wk | 52 (0.21) | 134 (0.27) | 0.77 | 0.56 | 1.07 | .12 |
| < 28 wk | 5 (0.02) | 32 (0.06) | 0.32 | 0.12 | 0.81 | .017 |

aOR, adjusted odds ratio; L, lower limit of 95% confidence interval; U, upper limit of 95% confidence interval.

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FIGURE 5
Run charts of weekly births, stillbirths and FGR by cLMP

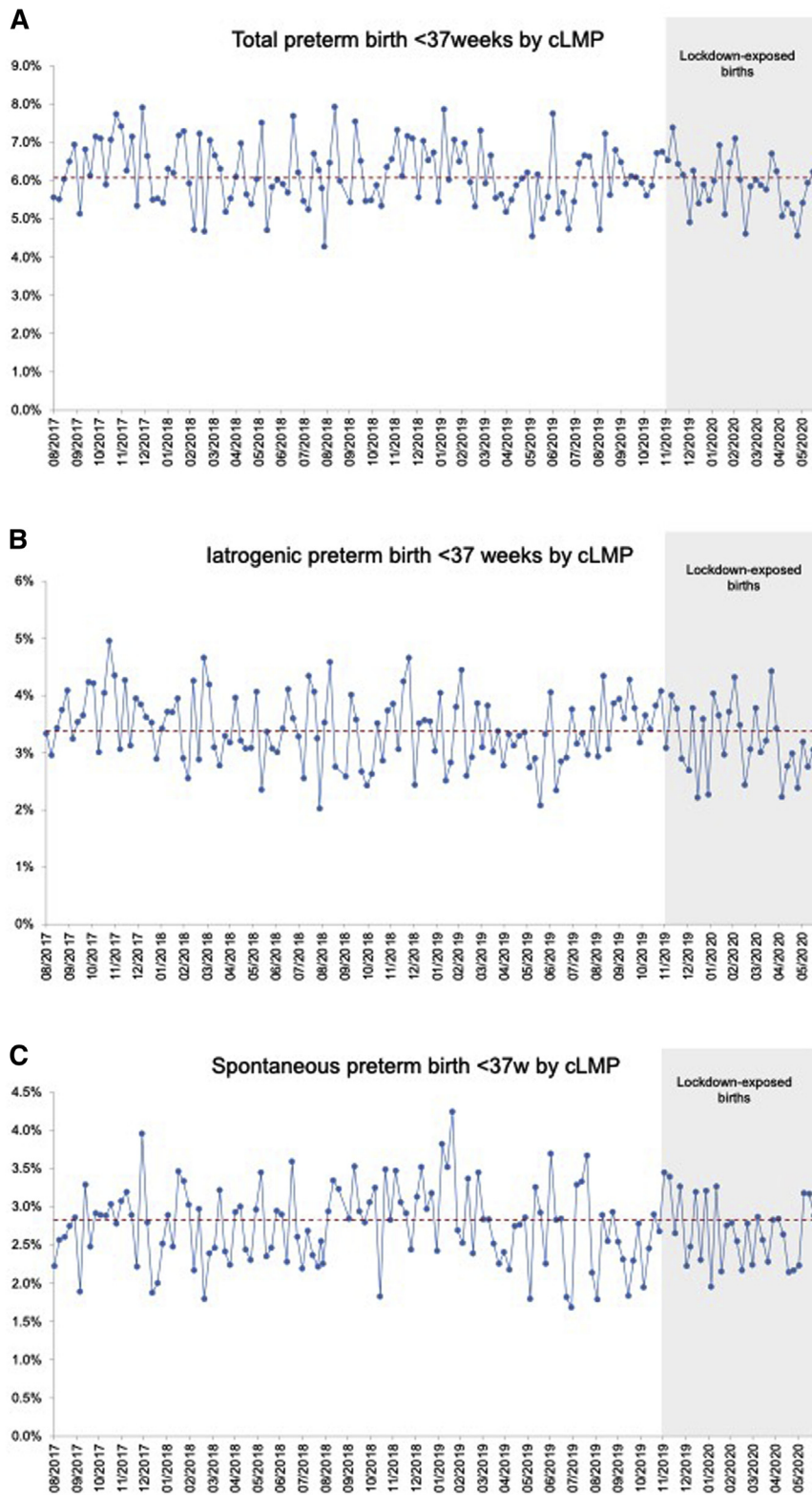


A, Weekly births by cLMP; B, Stillbirths by cLMP; C, FGR by cLMP.

cLMP, calculated last menstrual period; FGR, fetal growth restriction.

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FIGURE 6
Run charts of preterm births <37 weeks by cLMP

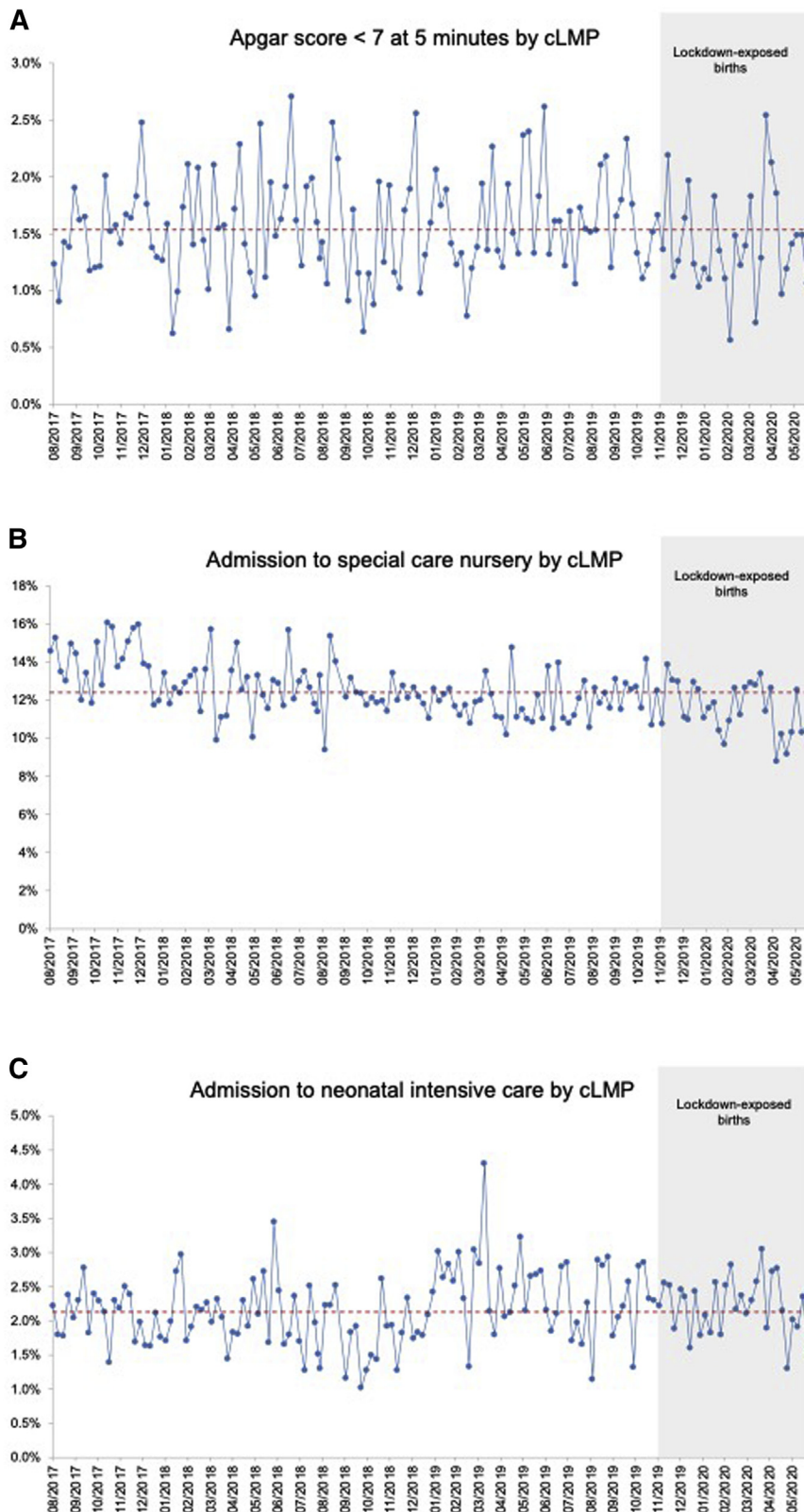


A, Total preterm birth by cLMP; **B**, Iatrogenic preterm birth by cLMP; **C**, Spontaneous preterm birth by cLMP.

cLMP, calculated last menstrual period.

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FIGURE 7
Run charts of newborn outcomes by cLMP

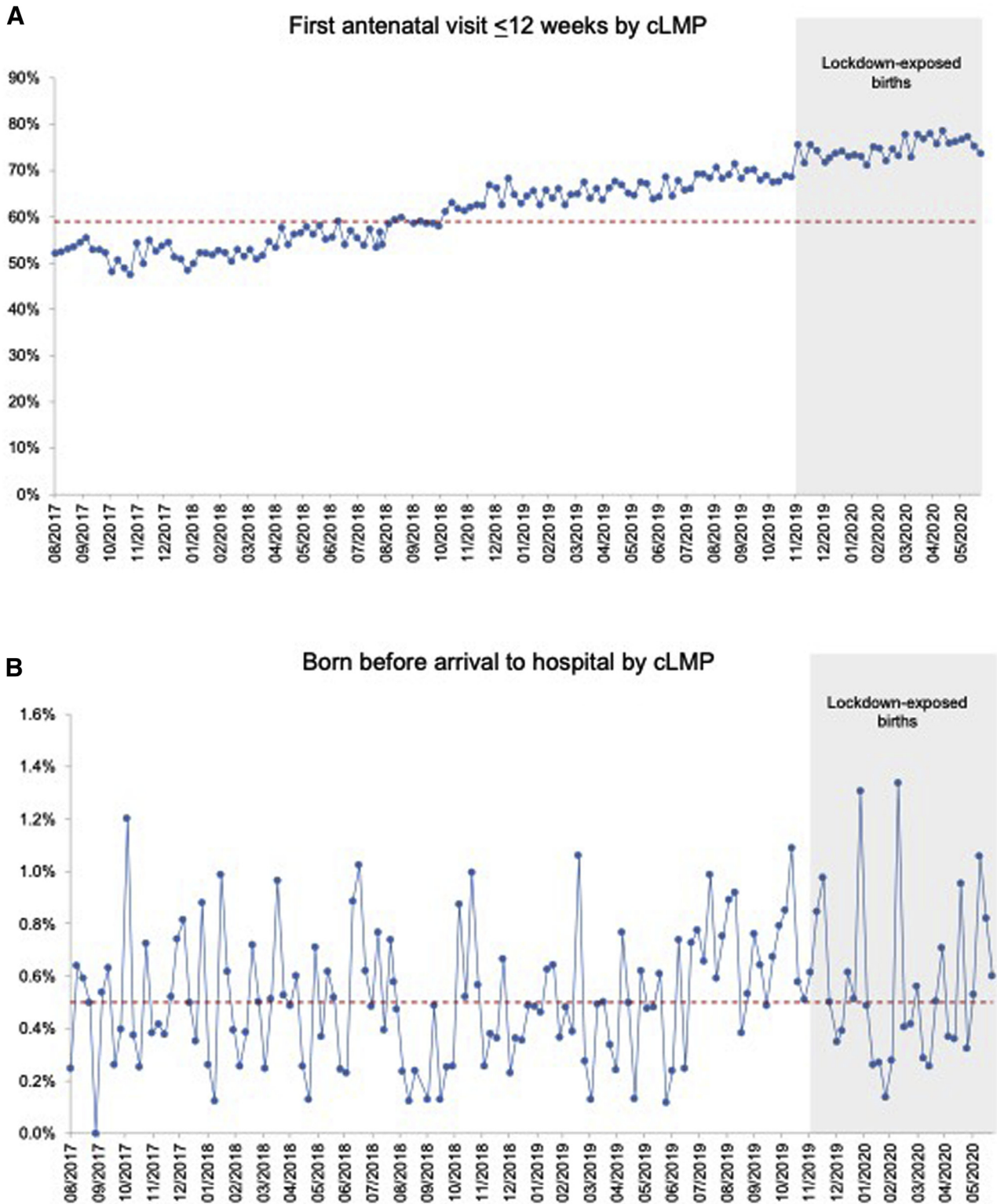


A, Apgar score <7 at 5 minutes; **B**, Admission to special care nursery; **C**, Admission to neonatal intensive care.

cLMP, calculated last menstrual period.

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FIGURE 8
Run charts of pregnancy care indicators by cLMP



A, First antenatal visit ≤ 12 weeks gestation by cLMP; B, Born before arrival by cLMP.
cLMP, calculated last menstrual period.

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lockdown in a high-income setting were less likely to have an iatrogenic PTB for suspected fetal compromise and more likely to have a preterm stillbirth. Health services, consumers, practitioners, and health policymakers must consider the consequences of our pandemic response on maternity care as we navigate the third year of the COVID-19 pandemic. ■

Acknowledgments

The health services and individual hospitals contributing to the Collaborative Maternity and Newborn Dashboard for COVID-19 pandemic are as follows:

- Mercy Health (Mercy Hospital for Women, Werribee Mercy Hospital)
- The Royal Women's Hospital, The Women's at Sandringham
- Monash Health (Monash Medical Centre, Casey Hospital, Dandenong Hospital)
- Northern Health (The Northern Hospital)
- Western Health (Joan Kirner Women's and Children's Hospital)
- Eastern Health (Box Hill Hospital, The Angliss Hospital)
- Peninsula Health (Frankston Hospital)

We thank the health service data managers and research midwives (Tania Fletcher, Lynn Rigg, Michelle Knight, Eleanor Johnson, Abby Monaghan, Pauline Hamilton, and Roshanee Perera) for their assistance with primary data collection and Mr Andrew Goldsachs for assistance with coding of the indications for iatrogenic births.

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Received March 7, 2022; revised April 3, 2022; accepted April 6, 2022.

L.H. has received research funding from Ferring Pharmaceuticals outside the scope of this work. B.W.M. is a consultant for Guerbet and has received research grants from Guerbet and Merck. K.R.P. has received consultancy fees from Janssen. D.L.R. has received fees from Alexion for participation in advisory boards unrelated to this work. All other authors declare no competing interests.

This study was funded by the Norman Beischer Medical Research Foundation and The University of Melbourne Department of Obstetrics and Gynaecology. L.H. and B.W.M. are supported by National Health and Medical Research Council investigator grants (GNT1196010 and GNT11766437). The funding bodies had no role in any aspect of the design or conduct of this study.

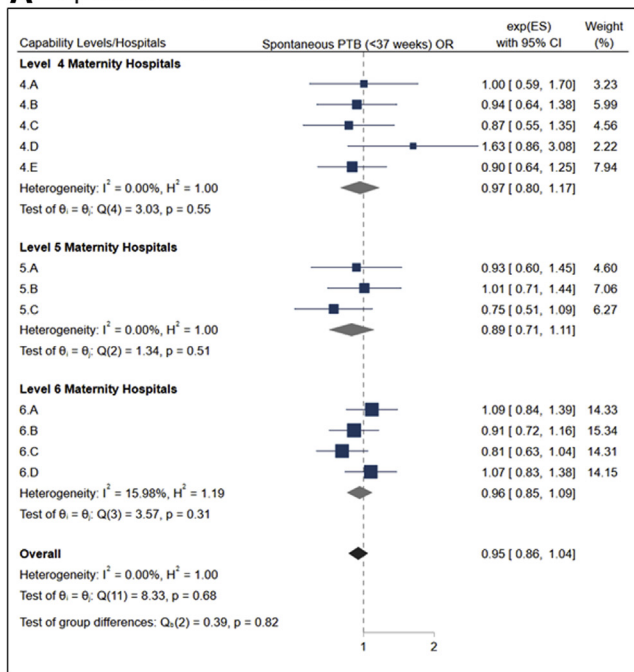
Nonidentifiable individual participant data are available on request from the Austin Health Human Research Ethics Committee (ethics@austin.org.au) and the Mercy Health Human Research Ethics Committee (ethics@mercy.com.au). The study investigators may contribute aggregate and nonidentifiable individual patient data to national and international collaborations whose proposed use of the data has been ethically reviewed and approved by an independent committee and following signing of an appropriate research collaboration agreement with The University of Melbourne.

The findings of this study were presented at the conference of the International Stillbirth Alliance and the International Society for the Study and Prevention of Perinatal and Infant Death, held virtually, November 12, 2021.

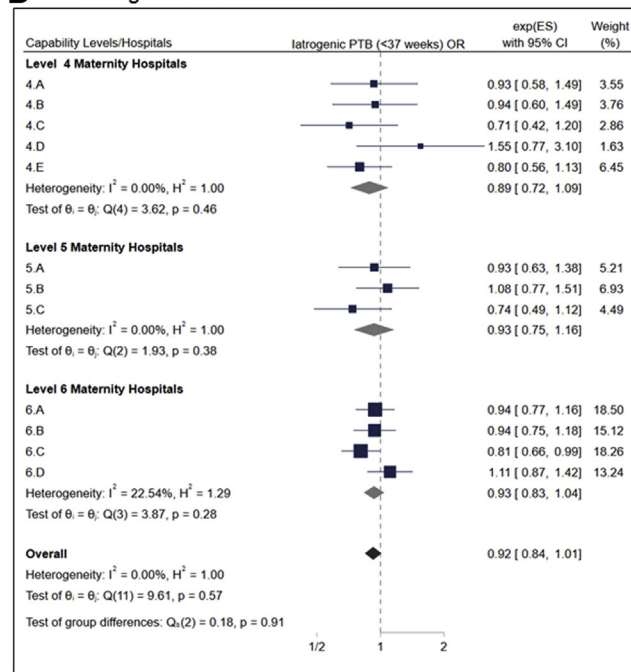
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SUPPLEMENTARY FIGURE S1
Forest plots for spontaneous iatrogenic preterm births*

A Spontaneous Preterm Births



B Iatrogenic Preterm Births



*used the multiple imputed dataset

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