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Original Research

Impact of COVID-19 mitigation measures on perinatal outcomes in the Netherlands

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A B S T R A C T

Objective: Investigate the acute impact of COVID-19 mitigation measures implemented in March 2020 on a comprehensive range of perinatal outcomes.
Study design: National registry-based quasi-experimental study.
Methods: We obtained data from the Dutch Perinatal Registry (2010–2020) which was linked to multiple population registries containing sociodemographic variables. A difference-in-discontinuity approach was used to examine the impact of COVID-19 mitigation measures on various perinatal outcomes. We investigated preterm birth incidence across onset types, alongside other perinatal outcomes including low birth weight, small-for-gestational-age, NICU admission, low-APGAR-score, perinatal mortality, neonatal death, and stillbirths.
Results: The analysis of the national-level dataset revealed a consistent pattern of reduced preterm births after the enactment of COVID-19 mitigation measures on March 9, 2020 (OR = 0.80, 95% CI 0.68–0.96). A drop in spontaneous preterm births post-implementation was observed (OR = 0.80, 95% CI 0.62–0.98), whereas no change was observed for iatrogenic births. Regarding stillbirths (OR = 0.95, 95% CI 0.46–1.95) our analysis did not find compelling evidence of substantial changes. For the remaining outcomes, no discernible shifts were observed.
Conclusions: Our findings confirm the reduction in preterm births following COVID-19 mitigation measures in the Netherlands. No discernible changes were observed for other outcomes, including stillbirths. Our results challenge previous concerns of a potential increase in stillbirths contributing to the drop in preterm births, suggesting alternative mechanisms.

Introduction

Coronavirus disease 2019 (COVID-19), an infectious respiratory disease, rapidly became a global pandemic in 2020. This event has not only strained global healthcare systems but has also disrupted societal structures and the world economy. To curb the disease's transmission, governments worldwide adopted a range of measures which restricted travel and the movement of people. The sudden onset of the pandemic and the rapid implementation of these mitigation measures presented a unique opportunity for a natural experiment, enabling researchers to study the consequences of these policies on health outcomes beyond the realm of COVID-19 infections.[1]

Evidence has emerged indicating that lockdown measures implemented during the early stages of the COVID-19 pandemic had an immediate impact on perinatal health, including reductions in preterm birth (PTB) incidence.[2–7] Overall, results from recent meta-analyses, reviews, and robust multi-country studies suggest that there is a pattern of reductions in PTB in high-income countries during the first three months of lockdowns.[6–9] However, evidence for other perinatal outcomes remains inconclusive.[7] Thus, there has been a call to continue

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the efforts to investigate whether the implemented measures had consequences beyond PTB.[7,8]

In the Netherlands, there have also been indications of a decline in PTB after the implementation of COVID-19 mitigation measures.[10,11] Using a quasi-experimental approach, the study by Been et al.[10] revealed a meaningful reduction in PTB incidence following the measures on March 9, 2020, where the strongest effect was observed two months after their enactment.[10] Although these findings provided valuable insights into the impact on PTB, the analyses were limited by datasets with restricted information on outcomes and maternal characteristics hindering a more comprehensive examination of PTB concerning its onset type (spontaneous vs. iatrogenic). Differentiating between these onset types is crucial for understanding the mechanisms behind the observed changes. If the reduction is mainly seen in iatrogenic PTB, it suggests that adjustments in healthcare practices played a significant role. Conversely, if the effect is primarily observed in spontaneous PTB, it indicates that environmental or behavioural changes may have contributed. The study by Klumper et al.[11] provided some indications that very PTBs in perinatal centres experienced a decline, especially those with an iatrogenic onset. However, it remains uncertain whether these findings can be extrapolated to a broader setting. Examining the impact on stillbirths (and perinatal mortality) is crucial due to concerns that the observed reduction in PTB quickly following the introduction of mitigation measures might be attributed to suboptimal care for high-risk pregnancies, potentially leading to an increase in stillbirths.[8,12]

In this study, we aim to overcome the limitations of Been et al. by utilizing the comprehensive Dutch Perinatal registry dataset (Perined). This dataset enabled us to conduct a more thorough evaluation of PTB categorized by their type of onset and to investigate research questions involving other perinatal outcomes. Thus, the primary goal of this study was to be able to validate the findings in Been et al. using a national-level dataset that contains both live and stillbirths. Moreover, we explored the immediate (acute) impact of COVID-19 mitigation measures implemented in March 2020 on a comprehensive range of perinatal outcomes.

Methods

Study Design

In this retrospective study, we conducted a difference-in-discontinuity analysis to investigate the acute impact of the national implementation of COVID-19 mitigation measures on a wide range of birth outcomes, using national-level routinely collected data from the Dutch Perinatal Registry (Perined).

COVID-19 mitigation measures in the Netherlands

The first recognized COVID-19 case in the Netherlands was confirmed in Noord-Brabant, one of twelve Dutch provinces, on 27 February 2020. Starting from 6 March, individuals residing in Noord-Brabant were advised to remain indoors if exhibiting potential COVID-19 symptoms. National-level measures were implemented on 9 March, followed by subsequent additions on 15 March and 23 March (available in Supplementary Table 1). The gradual relaxation of initial measures commenced on 1 June, allowing for the reopening of businesses under specified conditions and the resumption of school activities.

Data sources and participants

In this study, we made use of the data sources contained within the Data Infrastructure for Parents and Children (DIAPER).[13] DIAPER is a data source administered by the National Institute for Public Health and the Environment (RIVM) which links data from various sources, i.e., the Dutch Perinatal Registry (Perined) and microdata files from Statistics Netherlands (CBS).

We obtained data on all singleton births registered in Perined that occurred in the Netherlands between 1 January 2010 and 31 December 2020. Perined comprises information on maternal characteristics, pregnancy, delivery, and birth outcomes, covering 97% of all births in the Netherlands.[14] Gestational age, a key variable in this study, is estimated by using information on the last menstrual cycle and foetal scans to ensure accuracy.[15]

For this study, we excluded pregnancy trajectories whose ending was registered as termination of pregnancies. Moreover, multiple births were excluded due to their inherent increased risk of PTB, making their PTB risk less amendable to change following COVID-19 mitigation measures. We furthermore excluded births with registered gestational age below 24 + 0 weeks or above 41 + 6 weeks. Dutch national multidisciplinary guidelines advise against active management of babies born at gestational ages of less than 24 weeks and 0 days.[16,17] Records with missing data on key variables, i.e., gestational age and birth weight (or implausible values, i.e., <500g and >6,500g) were excluded from the analysis.

Outcomes

The outcomes were: Preterm birth (PTB), i.e., birth occurring before 37 + 0 weeks of gestation. Additionally, we investigated additional PTB sub-categories according to gestational age (24 + 0–25 + 6 weeks, 26 + 0–27 + 6 weeks, 28 + 0–31 + 6 weeks, and 32 + 0–36 + 6 weeks) and onset, i.e., spontaneous and iatrogenic. PTBs were considered ‘spontaneous’ if labour started with spontaneous preterm contractions and/or preterm prelabour rupture of membranes. PTBs after elective caesarean section or after induction of labour were considered to have an ‘iatrogenic’ onset. Low birth weight, birth weight below 2500 g. Small for gestational age, defined as birth weight below the 10th centile adjusted for gestational age and sex, according to national reference curves.[18] Neonatal intensive care unit (NICU) admission. Five-minute low APGAR score, i.e., 5-min APGAR score <7. Neonatal death, defined as death occurring up to 7 days after birth. Perinatal mortality, i.e., intrauterine death occurring after 24 + 0 weeks of gestational age or neonatal death up to 7 days after birth. Stillbirth, defined as intrauterine death occurring after 24 + 0 weeks of gestational age or death occurring during delivery.

Covariates

We obtained information on various maternal characteristics and demographic variables. Maternal age in categories (≤19, 20–34, ≥35 years), parity (nulliparous vs multiparous); equivalized household disposable income during the year of birth (corrected for size and composition of the household)[19] was categorized into low, medium and high where the low and high categories correspond to the lowest and highest quintiles, respectively; maternal migration background was used as defined by CBS (based on country of birth), i.e., Dutch, Turkish, Moroccan, Surinamese, Antillean, others western, and others non-western; mother’s highest educational level was classified as in CBS records as low (up to elementary education), medium (secondary education), high (higher education), or unknown.

Statistical analysis

We implemented a difference-in-discontinuity (diff-in-disc) design to assess the acute (immediate) effect of COVID-19 mitigation measures on perinatal health. Our approach, is a variation of the method by Grembi et al., making use of individual-level data instead of aggregated data.[20] A diff-in-disc approach is appropriate when the assignment to an intervention is based on a clear and arbitrary threshold—in our case, the date of birth corresponding to the enactment of COVID-19 mitigation measures. This quasi-experimental approach assumes that the intervention assignment for individuals close to the cut-off value will be "as-good-as-random" and a causal effect can be estimated by comparing outcomes for groups of individuals just above and below the cut-off. This method has been used in various settings to assess the impact of public health policy changes (e.g., Epure et al.).[21]

For the main analysis, we included data from children born two months before (January 9, 2020–March 8, 2020) and two months after the cut-off date of March 9, 2020 (March 10, 2020–May 9, 2020). This allowed us to remain close to the date of the measures' enactment while maintaining a reasonable sample size. The design compares outcomes from births occurring directly before versus directly after the cut-off date, similar to a regression discontinuity design. However, changes in outcomes around the cut-off may also be influenced by other factors, such as yearly seasonal patterns. To address this, the diff-in-disc design incorporates data from births occurring during the same periods in previous control years (the two-month windows around the cut-off date from a total of 10 years) that did not experience the intervention (borrowing elements from a difference-in-differences approach). By comparing the period surrounding the implementation of the measures in 2020 to the same time periods in years preceding the COVID-19 pandemic, the analyses account for underlying temporal trends, seasonal variation, and other potential time-variant factors. All cases included in our analyses were between 24 + 0 and 41 + 6 weeks of gestation at the time of birth, meaning they were conceived between the second and third quarters of 2020 (when there were no signs of the incoming epidemic). This corresponds to a relatively short and consistent time frame, with all exposed births occurring in the final half of the second trimester or the third trimester.

The diff-in-disc design exploits a threshold rule in the data-generating process and creates comparable populations with different exposure statuses just above and below a threshold. Unlike approaches such as interrupted time series (ITS), which measure intervention effects as differences in averages over the entire study period, the diff-in-disc approach analyses outcomes at the individual level and focuses on the change, or discontinuity, in effect near the cut-off point, making it especially suitable for detecting transient effects.

We employed logistic regression models for our analysis since our outcomes were binary. We divided the sample into cohort periods (one per year of available data) centered around the cut-off. The parameter of interest is the effect of the implementation of mitigation measures on the birth outcome variable in the different time windows before versus after March 9, 2020, relative to that observed before versus after the same date in previous and subsequent years. Due to the unpredictability of the timing of the implementation of lockdown measures, it is reasonable to assume that exposure assignment is not dependent on maternal and sociodemographic characteristics after accounting for seasonality and underlying trends. Inclusion of covariates in the models as being correlated to the outcome, should serve to improve the efficiency of the estimators.

We evaluated the key diff-in-disc assumptions.[20] A thorough description of the assumptions and the results of these checks are available in the Supplementary Materials. Other time windows (three and four months) are explored in sensitivity analyses. Additionally, we performed a sensitivity analysis by adjusting the intervention date for stillbirths to two weeks earlier than the date used for PTB. This adjustment aims to capture any stillbirths that might have occurred earlier due to the lockdown measures, which would otherwise be missed if both outcomes were evaluated concurrently. All analyses were performed using R version 4.2.3.[22]

Role of funding source

The funders of the study were not involved in the study design, data collection, data analysis, interpretation, or the writing of the manuscript.

Results

Between 2010 and 2020 there were 2,142,895 records in the Perined database. After the exclusion of multiple births, births <24 + 0 weeks or >41 + 6 weeks, and cases with missing data on key variables, data on 1,763,571 singleton births was available (Supplementary Fig. 1). The characteristics of the 2010–2020 population are shown in Supplementary Table 1. The main analysis included the births occurring two months before and after the cut-off date in March 2020, i.e., 50,237. Additionally, the analysis included the births that occurred in the same window for each of the available control years before 2020, leading to a total of 523,357 births used in the diff-in-disc for the two-month window (as reported in Tables 1 and 2). The number of births per year that were included in the main analysis can be found in Supplementary Tables 5–15.

It is a genuine concern that the analyses could be affected by changes in missing rates due to reporting issues during the pandemic period. However, we did not observe increased missingness for cases recorded during the pandemic period.

The population characteristics of exposed vs unexposed births were comparable, supporting the notion that births right below and above the cut-off (threshold) comply with the exchangeability assumption (available in Supplementary Table 2).

Table 1 shows the results from the diff-in-disc models for PTB. It was observed that the implementation of the 9 March measures was related to reductions in PTB birth across the two-month time window surrounding implementation, i.e., odds ratio (OR) 0.80 (95% confidence interval (CI) 0.68–0.96).

Regarding the onset of PTB, we observed an indication of a reduction in the odds of spontaneous PTB (OR [95%CI] = 0.80 [0.62–0.98]) after the implementation of the measures. For iatrogenic PTB, the point estimate also indicates a (smaller) reduction (OR = 0.91), however, the confidence intervals for this estimate cover the null (0.67–1.23).

Table 2 displays the results of the diff-in-disc models concerning perinatal outcomes. While there is some suggestion of reduced odds for low birth weight (OR [95% CI] = 0.89[0.74–1.07]) following the implementation of the measures, it's essential to note that the confidence intervals for this outcome include the null value. Regarding stillbirths, our analysis did not yield compelling evidence of a substantial change following the implementation of the measures (OR [95% CI]

Table 1
Acute impact of COVID-19 mitigation measures introduced on March 9, 2020 on preterm birth (±2 months' time window) n = 523,357.

	OR	95% CI
Preterm birth	0.80	0.68–0.96
By gestational age		
32 + 0 to 36 + 6	0.80	0.68–0.98
28 + 0 to 31 + 6	0.73	0.43–1.26
26 + 0 to 27 + 6	0.85	0.30–1.39
24 + 0 to 25 + 6	0.82	0.15–1.49
By type of onset		
Spontaneous	0.80	0.62–0.98
Iatrogenic	0.91	0.67–1.23

Table 2
Acute impact of COVID-19 mitigation measures introduced on March 9, 2020 on perinatal outcomes (±2 months' time window), n = 523,357.

Outcome	OR	95% CI
Small for gestational age	0.98	0.86–1.11
Low birth weight	0.89	0.74–1.07
Low APGAR (5 min)	0.95	0.71–1.26
NICU admission	1.00	0.77–1.31
Stillbirth	0.95	0.46–1.95
Perinatal mortality	0.80	0.44–1.47
Neonatal death	0.53	0.19–1.47

= 0.95 [0.46–1.95]). For the remaining outcomes we examined, there was no indication of a substantial shift following the implementation of mitigation measures. The outcomes from models utilizing three and four-month windows aligned with those from the primary analysis (Supplementary Materials, Table 4). There was no evidence of a substantial change in stillbirths after the implementation of the measures when, in a sensitivity analysis, the intervention date was set to two weeks earlier than the date used for PTB (OR = 1.04, 95% CI = 0.50,2.15). This conclusion is in line with the findings from the main analysis.

Discussion

In this comprehensive nationwide quasi-experimental study, our findings revealed a decrease in the odds of PTB after the introduction of the initial COVID-19 mitigation national mitigation measures in the Netherlands. When PTBs were further examined by their onset type, a meaningful reduction in spontaneous PTBs was observed, though the evidence for iatrogenic births was less conclusive. As for stillbirths, our analysis did not yield compelling evidence of a substantial change following the implementation of these measures.

To the best of our knowledge, this work represents the largest study within a European context that utilizes a robust quasi-experimental approach to evaluate the acute impact of early COVID-19 mitigation measures on a comprehensive array of perinatal outcomes. Our findings regarding PTB align with prior research, demonstrating a reduction in PTBs within high-income countries between two and four months following the initial implementation of lockdown measures.[7,8] Importantly, the estimates for PTB closely mirror those reported in the study by Been et al.[10] The odds ratios in both papers are nearly the same, and all estimates follow a similar pattern.

Our study builds upon previous research by delving deeper into the impact of mitigation measures on spontaneous and iatrogenic PTB as distinct categories. This differentiation provides further insight into the likely mechanisms through which lockdown measures may have influenced the observed reduction in PTB. The results that spontaneous PTB seems to be driving the observed changes in the overall PTB rates are in line with the observations from the largest multi-country study.[8] The observed reductions in spontaneous PTB are of considerable magnitude. We are unaware of any other single intervention that has shown a similar level of effectiveness in reducing PTB at the population level in high-income settings. It is noteworthy, however, that our findings diverge from those reported by Klumper et al.,[11] where they observed that the decline in very PTBs born in perinatal centres (facilities with Neonatal Intensive Care Units, NICU), was primarily driven by births with an iatrogenic onset. Unfortunately, due to privacy constraints within the DIAPER infrastructure, we lack information regarding whether the births occurred in facilities with a NICU. Future research may explore whether any shifts occurred in obstetric practices or the healthcare-seeking behaviour of pregnant women, which correspond to the key mechanisms that could explain any potential changes in iatrogenic births.[23]

Regarding stillbirths, our analysis did not reveal substantial evidence of a change in their occurrence following the implementation of the mitigation measures. A main concern raised by several researchers when countries began reporting a decrease in PTB rates was the possibility of a compensatory increase in stillbirths.[8,12] Our findings are in line with the results from previous European studies that have not observed considerable changes in stillbirths following the implementation of measures.

The causes of spontaneous PTB, which make up about two-thirds of all PTB, remain largely unclear and are likely influenced by multiple factors. This complexity hinders the development of effective preventive strategies. It's worth noting that many of the known risk factors for PTB could potentially be influenced by the implementation of COVID-19 mitigation measures.[24,25] The timing of the observed reductions in PTB in our study suggests that improved hygiene practices and proactive behavioural changes may have played a role. Furthermore, the closure of businesses and the transition to obligatory home-based work likely resulted in less physically demanding work, reduced shift work, lower work-related stress, improved sleep duration, increased maternal exercise both indoors and outdoors, and enhanced social support networks—all factors that could positively impact pregnancy outcomes.[3] Additionally, significant reductions in air pollution have been documented following COVID-19 mitigation measures, including in the Netherlands.[26] The decline in pollution levels may have contributed to the observed reductions in PTB [27,28].

In summary, in this national quasi-experimental study we found further evidence of a reduction in PTB following the implementation of COVID-19 mitigation measures in the Netherlands, particularly for spontaneous PTBs. When considering these results alongside preliminary evidence from other countries, opens up avenues for the exploration of innovative preventive approaches for PTB [27,28].

Ethical approval

This study used registry data. No ethical approval was required. Perined, CBS, and RIVM approved the corresponding data requests.

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Competing interests

This project was funded by ZonMW, Chiesi Pharmaceuticals, de Snoo-van 't Hoogerhuijs Foundation, and Strong Babies. The funders of the study were not involved in the study design, data collection, data analysis, interpretation, or the writing of the manuscript.

Data sharing

The authors are open to sharing the syntax for the statistical analysis. This study is based on registry data from the Dutch Perinatal Registry (Perined, https://www.perined.nl/onderwerpen/onderzoek/gegevensaanvragen) and microdata from Statistics Netherlands (https://www.cbs.nl/nl-nl) accessed via the RIVM DIAPER Infrastructure (https://www.rivm.nl/monitoren-zwangerschap-en-geboorte/diaper). Access to linked electronic health and sociodemographic records requires approval from the data providers, i.e., RIVM, Perined, and Statistics Netherlands. Information on data requests can be found on their respective websites.

Contributors

JVB, CG, LBO, SO, LB obtained funding for the study. All authors were involved in conceiving the study. LBO and LCMB analysed the data. All authors were involved in interpreting the data. LBO and LCMB drafted the manuscript. JVB NB BG SO ASR JS JL CG provided additional input at the writing stage. All authors read and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2024.09.002.

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