Associations of COVID-19 lockdown with gestational length and preterm birth in China

Moran Dong[1], Rui Qian[1], Jiaqi Wang[1], Jingjie Fan[1], Yufeng Ye[1], He Zhou[1], Brian Win[1], Eve Reid[1], Suijin Zheng[1], Yanyun Lv[1], Yudong Pu[1], Hanwei Chen[1], Juan Jin[1], Qingmei Lin[1], Xiaoyang Luo[1], Guimin Chen[1], Yumeng Chen[1], Zhongrong He[1], Guanhao He[1], Shouzhen Cheng[1], Jianxiong Hu[1], Jianpeng Xiao[1], Wenjun Ma[1], Tao Liu[1], and Xiaozhong Wen[1]

[1]Affiliation not available

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Abstract

Objective:to examine the associations of COVID-19 lockdown with gestational length and preterm birth (PTB). Design: Hospital-based retrospective study. Setting: All hospitals in Foshan (n=62) and several other hospitals in Guangzhou (n=1), Shenzhen (n=1), Dongguan (n=2), and Jiangmen (n=1) in Guangdong Province, China were selected. Population and Methods: A total of 595396 singleton live infants born between 2015 and 2020 were included. The exposed group (N=101900) included women who experienced the COVID-19 Level I lockdown (1/23-2/24/2020) during pregnancy, while the unexposed group (N=493496) included women who were pregnant during the same calendar months in 2015-2019. Cumulative exposure was calculated based on days exposed to different levels of emergency responses with different weighting [1/22/2020 or earlier (no response, weighting=0), level I (weighting=3), 2/25-5/9/2020 (level II, weighting=2), and 5/10-12/31/2020 (level III, weighting=1)]. Main outcome measures: demographics, lockdown exposure, preterm birth, gestational week. Results: The exposed group had a shorter mean gestational length than the unexposed group (38.66 vs 38.74 weeks: adjusted β=-0.06 week [95%CI, -0.07, -0.05 week]). The exposed group also had a higher risk of PTB (5.7% vs 5.3%; adjusted OR=1.08 [95%CI, 1.05, 1.11]). These associations seemed to be stronger when exposure occurred before or during the 23rd gestational week (GW) than during or after the 24th GW. Conclusions: The COVID-19 lockdown measures were associated with a slightly shorter gestational length and a moderately higher risk of PTB. Early and middle pregnancy periods may be a more susceptible exposure window. Funding: National Natural Science Foundation of China.

Introduction

The ongoing COVID-19 pandemic has spread throughout the world and affected billions of people(1). Various measures have been implemented around the world to control the pandemic, including restricting large social movements and gatherings, closing international and interstate borders, controlling travel, and implementing partial or full lockdown of cities and regions. These measures have effectively controlled the spread of COVID-19 and reduced the anthropogenic emissions of air pollution (2), which have resulted in substantial health benefits (3). However, these measures have also caused huge economic loss, unemployment, shortage of medical resources, and psychological stress, (4-7) which may lead to adverse health outcomes.

Pregnant women and fetuses may be susceptible populations to the effects of lockdown and restriction measures. A few studies have reported that the COVID-19 lockdown measures may increase the risk of adverse birth outcomes such as stillbirth and cesarean delivery (8,9). Preterm birth (PTB) is one of the most important adverse birth outcomes and a major cause of death in children under 5 years of age(10). Several studies have examined the associations of COVID-19 lockdown measures with the risk of PTB, but

the results were inconsistent(8,9,11-14). A study in London reported an increase in the incidence of PTB during the COVID-19 pandemic period over the pre-pandemic period(12). Another study conducted in Nepal also observed a greater risk of PTB during the COVID-19 lockdown than before lockdown.(8) In contrast, studies conducted in Denmark and the Netherlands observed a substantial reduction in the risk of PTB during the COVID-19 periods than before lockdown (11,13). The other two studies conducted in China and Botswana did not find any significant association between the COVID-19 lockdown and the risk of PTB (9,14). The inconsistent findings across these studies may be attributable to differences in study design, sample size, demographic characteristics of study subjects, and socioeconomic developments of societies.

Although the aforementioned studies have preliminarily estimated the associations between COVID-19 lockdown and PTB, several research issues or gaps need to be addressed. First, the susceptibility of pregnant women to environmental factors largely depends on the stage of pregnancy (15,16). Previous studies estimated the overall rate of PTB in pregnant women exposed to COVID-19 lockdown measures (8,9,11,12,14,17-19), but did not consider their pregnancy stage when lockdown occurred. This may lead to an underestimation of PTB risk during the lockdown if pregnant women with a gestational age > 36 weeks were also included. Second, lockdown intensity usually varied over time. However, none of previous studies considered the change in intensity of lockdown exposures. Third, previous studies have suggested a seasonal variation in the incidence of PTB (20,21). The seasonal effects should be considered in selecting the control periods for the COVID-19 lockdown. However, some previous studies applied the annual or multiple years' average incidence of PTB as the reference (9,11,14), which might lead to biased findings. Fourth, the follow-up time (2-4 months) in previous studies was not long enough to capture the birth outcomes of pregnant women who experienced the lockdown in their early pregnancy (8,9,11,12,14).

To fill these research gaps, we comprehensively elucidated the association of the COVID-19 lockdown on gestational length and PTB risk in South China by quantifying the timing and intensity of exposure, considering seasonal effects, and allowing sufficient follow-up time. This study could provide in-depth insights to inform management practices regarding pregnancy and childbirth during and after lockdown.

Methods

Study settings and subjects

We selected all hospitals in Foshan (n=62) and several other hospitals in Guangzhou (n=1), Shenzhen (n=1), Dongguan (n=2), and Jiangmen (n=1) in Guangdong Province, South China, as study settings (Figure 1 - Map). All hospital birth data from 1/1/2015 to 12/31/2020 were collected (n=749059). Birth records with multiple births (n=27659), stillbirths (n=726), or missing information on key variables (n=2883) were excluded. Moreover, 122395 births were excluded because their pregnancy did not overlap with the COVID-19 lockdown in 2020 or the same calendar months in 2015-2019. Finally, 595396 mother-newborn pairs were included. None of these women had a positive SARS-CoV-2 test result (Figure S1 - Flowchart).

Data collection

The following information on each birth was extracted from the hospital information system or birth record system: infant sex, date of birth, delivery type (vaginal or cesarean), gestational weeks (GW) at birth, maternal age, parity, pregnancy complications such as hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM), and major adverse pregnancy outcomes such as miscarriage and stillbirth. We carefully checked the accuracy and quality of source data. Implausible values and outliers were either corrected or recoded as missing.

Exposure assessment

The National Emergency Response Plan for Public Emergencies by the China State Council defined 4 levels of emergency response: Level I (extremely serious), Level II (serious), Level III (relatively serious), and Level IV (common) (22). After the outbreak of COVID-19, the Guangdong Provincial Government announced a Level I response on 1/23/2020 and later degraded the response level to Level II and Level III on 2/24/2020 and 5/9/2020, respectively. The Level III response was maintained after 5/9/2020. During the Level I response,

offices, shops, colleges, schools, childcare facilities, and all other non-essential institutions were shut down. Residents' social activities and gathering were rigorously restricted. Most of the workforce adapted to a new work-from-home mode due to traffic and mobility restrictions. Fewer restriction measures were implemented during the Level II and Level III responses. During the Level II response, crowded areas were temporarily closed and disinfected before reopening. During the Level III response, people's lives gradually returned to normal. All shopping malls, supermarkets, hotels, restaurants, and other living areas were reopened with routine precautionary measures such as wearing masks and practicing social distancing (Table S1).

We defined the time period with a Level I response (1/23-2/24/2020) as Level I lockdown. Women who were pregnant during the Level I lockdown period were defined as the exposed group (N=101900). Women who were pregnant during the same calendar months in 2015-2019 were defined as the unexposed group (N=493496). This served to control for the seasonal effect, as our data indicated a significant variation in PTB rate across calendar months of conception (Figure S2).

To further explore the potential susceptible exposure window, we divided the exposed group into 11 subgroups according to their GW on 1/23/2020. We determined the day of conception based on the gestational length and date of birth. For example, women who were conceived during the Level I lockdown period were defined as the first subgroup, and women whose GWs were less than four weeks on 1/23/2020 were defined as the second subgroup (Figure S3). The gestational age of women with over 41 GWs was grouped into 41 weeks. Similarly, the unexposed group was divided into correspondingly matching subgroups. With each pair of subgroups (exposed vs unexposed), we estimated the associations of lockdown exposure with gestational length and PTB.

Restriction measures during the Level II and Level III responses may also have adverse effects on PTB risk. Therefore, we quantitatively estimated individual cumulative exposure dose to lockdown by assigning different weightings to days with different levels of emergency responses: 1/22/2020 or earlier (no response, weighting=0), 1/23-2/24/2020 (Level I, weighting=3), 2/25-5/9/2020 (Level II, weighting=2), and 5/10-12/31/2020 (Level III, weighting=1). Moreover, to account for the potential effect modification by timing of exposure, we only estimated the cumulative exposure dose in their first 22 GWs, a conventional cut-off value of the shortest GW for a newborn to survive with current medical technology (Figure 2) (23). The distribution of the lockdown exposure dose in the exposed group is shown in Figure S4.

Outcome measures

According to the World Health Organization, PTB was defined as gestational length [?] 37 completed weeks (24). Moderate PTB (MPTB) was defined as gestational length between 32 and 36 completed weeks. Very PTB (VPTB) was defined as gestational length < 32 completed weeks. The VPTB included extremely PTB (gestational length < 28 completed weeks).

Potential confounders

The following variables were considered as potential confounders: maternal age, marital status, parity, residential district, delivery type, and infant sex. These variables were selected based on biological plausibility, literature review, and availability of information.

Potential mediators

To facilitate interpretation of our findings regarding the association between COVID lockdown and preterm birth, we considered pregnancy complications (HDP and GDM) and changes in air pollution around lockdown beyond regular seasonal variation as two potential mediators. HDP included gestational hypertension, preeclampsia/eclampsia, chronic hypertension, and chronic hypertension with superimposed preeclampsia (25,26) (Table S2). Daily air pollutant (PM_{10}, $PM_{2.5}$, NO_2, SO_2, and CO) data in the selected cities during 2015-2020 were collected from the National Urban Air Quality Real-time Publishing Platform (*http://106.37.208.233:20035/*). The average air pollutant concentrations during, after the Level I lockdown in 2020, and during the same calendar months in 2015-2019 were calculated.

Statistical analysis

A Chi-square test was used to assess the differences in socio-demographic and pregnancy characteristics between the exposed and unexposed groups. A generalized linear model (GLM) was applied to estimate the associations of Level I lockdown exposure with gestational length (linear regression) and PTB risk (binary logistic regression), after adjusting for potential confounders. A multinomial logistic regression model was used when PTB was further divided into MPTB and VPTB, with term birth as the reference. An interaction test was conducted to examine the potential modification effects of infant sex by comparing the association coefficients between male and female infants (27).

Similarly, GLM and multinomial logistic regression models were employed to examine the association of cumulative exposure dose with gestational length or PTB. The cumulative exposure dose in the exposed group was divided into four groups by quartiles (Q1, Q2, Q3, and Q4). The association of each quartile of cumulative exposure (vs unexposed) with gestational length or PTB were estimated. A trend test was conducted by assuming the values of quartiles as a continuous variable.

All analyses were performed using R3.6.1 (R Development Core Team 2019, https://www.r-project.org). All the tests were two-sided and a $P<0.05$ was considered to be statistically significant.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

General characteristics of study participants

Out of the 595396 women included, 101900 (17.1%) were in the exposed group and the other 493496 (82.9%) were in the unexposed group (Table 1). The exposed group had higher proportions of participants older than 30 years (52.8% vs 49.4%), with GDM (15.4% vs 12.3%), multiparity (21.8% vs 15.9%), and natural delivery (62.2% vs 60.3%), but a lower proportion of HDP (2.3% vs 2.7%) than the unexposed group.

Associations of COVID-19 lockdown exposure with gestational length

The exposed group had a shorter gestational length than the unexposed group (38.66±1.46 weeks vs 38.74±1.46 weeks). The Level I response (vs no exposure) was significantly associated with a 0.06 (95%CI: 0.05, 0.07) week decrease in gestational length in the total study sample after adjusting for confounders (Table 2). Subgroup analyses showed significant associations between lockdown exposure and decreased gestational length only among pregnant women whose gestational ages were <24 GWs or 28^{th}-31^{st} GWs on the first day of lockdown (1/23/2020). The mean difference varied between -0.11 and -0.04 weeks.

We observed a negative association between cumulative lockdown exposure dose and gestational length (Table 2). Each 100 unit increase in the cumulative exposure dose during the first 22 GWs was associated with a 0.05 (95%CI: 0.04, 0.06) week decrease in gestational length, after adjusting for confounders. In addition, compared to the unexposed group, the Q1, Q2, Q3 and Q4 quantiles of cumulative exposure were associated with 0.09 (0.07, 0.11), 0.13 (0.11, 0.16), 0.14 (0.11, 0.16), and 0.09 (0.07, 0.11) weeks decrease in gestational length, respectively.

Associations of COVID-19 lockdown exposure with PTB

A higher PTB rate (5.7% vs 5.3%) and MPTB rate (5.2% vs 4.9%) were observed in the exposed group compared to the unexposed group in the total sample. Significant increases in PTB risk (adjusted OR=1.08, 95%CI: 1.05, 1.11) and MPTB risk (adjusted OR=1.09, 95%CI: 1.05, 1.12) were also observed after adjusting for confounders (Table 3). However, the association between lockdown and VPTB was not statistically significant (adjusted OR=1.04, 95%CI: 0.94, 1.16). Subgroup analyses showed significant associations of lockdown exposure with increases in PTB and MPTB only among pregnant women <24 GWs on the first day of lockdown. The OR values varied between 1.10 and 1.20 for PTB and MPTB.

We also observed a positive association between cumulative exposure dose to lockdown and PTB risk (Table 3 and Table S3). Each 100 unit increase in the lockdown exposure during the first 22 GWs was significantly associated with 1.07 (95%CI: 1.05, 1.09), 1.07 (1.05, 1.08), and 1.12 (1.06, 1.18) times higher risks in PTB, MPTB, and VPTB, respectively. The adjusted ORs of PTB for the Q1, Q2, Q3 and Q4 quartiles of cumulative exposure (vs no exposure) were 1.16 (1.08, 1.23), 1.22 (1.14, 1.30), 1.14 (1.07, 1.22), and 1.19 (1.11, 1.27), respectively.

Effect modification by infant sex in the associations of lockdown exposure with gestational length and PTB

Subgroup analyses showed similar associations of Level I lockdown with gestational length [adjusted β=-0.06 (95%CI: -0.08, -0.05) week vs adjusted β= -0.06 (-0.08, 0.05) week] or risk of PTB [adjusted OR=1.09 (95%CI: 1.04, 1.14) vs adjusted OR=1.08 (1.03, 1.13)] in male infants and in female infants (Table 4). There were no significant sex interaction (P>0.05) in these associations.

Discussion

Main Findings

This study comprehensively examined the associations of the COVID-19 lockdown with gestational length and risk of PTB using a large database from South China. We found that the lockdown exposure was significantly associated with a slightly shorter gestational length and a moderately higher risk of PTB. These associations were greater among women who were in early or middle pregnancy during the Level I lockdown period. There were also significant exposure-response associations of higher cumulative exposures to lockdown with a shorter gestational length and an increased risk of PTB.

Interpretation

Our finding of a positive association between the COVID-19 lockdown and risk of PTB was consistent with some previous studies (8,12,28). Several reasons possibly explained the increased risk of PTB. First, the lack of medical resources during the COVID-19 pandemic and lockdown measures might interrupt the timely antenatal care for pregnant women (9,29). Secondly, fear and panic about the pandemic could make pregnant women reluctant to seek help from medical institutions, and further impacted the timely detection and diagnoses of pregnancy complications (9,30). For example, we observed a higher rate of GDM in the exposed group than the unexposed group. This suggested a potential mediation role of GDM, as GDM is a critical risk factor of PTB (10). In addition, pregnant women have always been considered a susceptible population to mental disorders (31). The lockdown and restriction measures could increase psychological problems in pregnant women through concomitant financial problems and increased stress (30,32), particularly if they were socioeconomically disadvantaged (33). The closure of entertainment venues also reduced the outlets for negative feelings (34). A previous study observed a more pronounced increase in depression and anxiety in pregnant women during the COVID-19 pandemic than in the general population (35). Lastly, the nutritional status of pregnant women was also of concern. During the lockdown period, the decreased supply of fresh foods could lead to inadequate intake of vegetables and high-fiber foods. Meanwhile, the intake of high-carbohydrate foods might have increased because they were relatively easier to obtain and store (9). It was reported that the overweight and obesity rates increased during the lockdown period due to unbalanced diets and less exercise (36). This suggested that the maternal stress and obesity during the lockdown might influence the risk of PTB (9,35).

We further observed that women in early and middle pregnancy during the Level I lockdown had a greater risk of PTB, which also contributed to the health effects of the COVID-19 lockdown. Zhang et al. reported that women in the first and second trimesters of pregnancy during the lockdown had more severe psychological disorders (16). A simple explanation could be that these mothers continued to experience Level II and III lockdown after the Level I lockdown, which may have led to more cumulative effects on their fetal health. This was supported by our observed positive association between PTB risk and cumulative exposure to lockdown of all levels in the first 24 GWs. An alternative explanation could be that early and middle

pregnancy is a critical period for fetal development because the majority of fetal organ and tissues retain plasticity at that time (37). As a result, lockdown-induced poor diet, depression, and anxiety problems in early and middle pregnancy may substantially interrupt fetal development (38-40).

It should be noted that several other previous studies reported a reduction (rather than an increase as in our study) in rate of PTB during the COVID-19 lockdown (11,13). Although the mechanisms underlying these negative associations were unclear, several socio-environmental and behavioral modifiers were proposed (5,41). First, the lockdown measures increased company and support from partners and family, which could reduce the existing psychological stress in pregnant women. Second, working from home increased their rest time at home and decreased work-related stress. Third, the reduced anthropogenic emissions improved the air quality, which could benefit maternal and fetal health. Fourth, precautionary behavioral changes were promoted during the lockdown, including social distancing, enhanced hand hygiene, and use of face masks. These behavioral changes could potentially reduce the chances of other common viral infections in addition to COVID-19 during pregnancy. Finally, lockdown measures also reduced daily commuting, road traffic incidents, and consumption of cigarettes, coffee, alcohol, prescription drugs, and street drugs due to limited accessibility (5,41).

Previous studies reported inconsistent associations of lockdown exposure with maternal and fetal health (5,11,13). These inconsistencies may have a few explanations. First, some studies (11) had small sample sizes and potentially inadequate statistical power to detect an association between lockdown exposure and PTB. Second, the seemingly decreased risk of adverse pregnancy outcomes related to lockdown might be partially related to the reduced number of ultrasound scans and screening, which increased the possibility of under-diagnoses of early pregnancy loss, miscarriages, or stillbirths. Third, the health effects of lockdown may last for several months, but previous studies did not track participants long enough to assess the total effects of lockdown, which could have led to underestimations. In this study, we used the data of pregnant women who experienced the Level I lockdown until the end of 2020 and were able to obtain birth outcomes of all exposed women by covering the entire pregnancy. Fourth, air quality improvement during the lockdown was proposed as a major contributor to the reduced risk of PTB. In this study, we also found a substantial reduction in air pollution during the lockdown (Table S4), which was consistent with previous studies (2,42). Fifth, seasonal effects and pregnancy stages were not considered in most previous studies, which could lead to biased results. To evaluate this potential bias, we estimated the difference in PTB rates between new births during the Level I lockdown and all previous births during the entire years (rather than matching the calendar months) from 2015-2019. We did not find a significant association between lockdown and PTB risk (Table S5). Finally, although the lockdown measures may increase company and support from partners and family, the potential increase in family conflicts and domestic abuse should also be considered (43). These findings suggest that the health effects of COVID-19 lockdown were comprehensively affected by socio-environmental changes and behavioral modifications, and that improvement in one factor could not make up for the overall disadvantage (11,28).

Strengths and Limitations

We applied a large dataset with detailed individual information to investigate the association between lockdown and PTB risk. The dataset covered a wide enough time, in which birth outcomes of all women who have experienced the lockdown were recorded. We used strict contemporaneous controls to reduce the impact of seasonal effects on birth outcomes. In addition, we quantified the cumulative exposure by designing weightings to quantitatively aggregate the effects of different phases of lockdown measures. These strengths could provide a stronger causal argument for our findings.

There were several limitations that need to be addressed. First, as the COVID-19 pandemic and associated lockdown measures occurred unanticipatedly, we had to collect data from medical records that might miss some other gestation-length-related outcomes such as early pregnancy losses, miscarriages, and stillbirths. Previous studies reported an increased rate of stillbirth related to the COVID-19 lockdown (8,12). Our supplemental analysis also showed a higher stillbirth risk in the exposed group than in the unexposed group (Table S6). Second, several individual behaviors such as smoking, alcohol consumption, nutrition, and

physical activity were not obtained. Their potential mediation roles were not evaluated in our analyses. Third, this study was conducted in only five cities in South China, which limited the generalization of our findings. Fourth, due to the coexistence of the COVID-19 pandemic and the lockdown status, we could not separate their induvial impacts on the outcomes.

Conclusion

Within a large dataset of birth records from South China, we found that COVID-19 lockdown was associated with a slightly shorter gestational length and a moderately higher risk of PTB. Early and middle pregnancy might be a more susceptible exposure window. The COVID-19 control measures were implemented in many countries to reduce the spread of infections and related morbidities. Meanwhile, the incidence of PTB remains high globally, and options for the prevention of PTB are very limited (44). Our findings suggest more attention and efforts are needed to support pregnant women during the lockdown, particularly for those with previous PTB as they are more susceptible (45). Health professionals should make appropriate and timely treatment decisions for pregnant women during the lockdown.

Contribution to Authorship

TL, WM, and XW designed the study; TL, MD, RQ, JW, JF, and YY analyzed the data, interpreted the results, and drafted the manuscript; RQ, JF, YY, SZ, YL, YP, HC, JJ, QL, XL, GC, YC, ZH, GH, SC, JH, and JX collected and cleaned the data; TL, BW, ER, WM, and XW edited the manuscript; All authors approved the final draft of the manuscript. TL and WM verified the underlying data. WM and XW are the study guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Disclosure of Interests

All authors declare no competing interests.

Data sharing

The statistical code and meta data are available from the corresponding author upon request.

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Ethics

This study was approved by the Ethics Committee of Guangdong Provincial Center for Disease Control and Prevention (No. W96-027E-2020004). The data analysis was carried out at a population level after data aggregation.

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References

(1) Johns Hopkins University of Medicine. COVID-19 Case Tracker. Follow global cases and trends. 2020.*https://coronavirus.jhu.edu/*(accessed Feb 22, 2021).

(2) Rodríguez-Urrego D, Rodríguez-Urrego L. Air quality during the COVID-19: $PM_{2.5}$ analysis in the 50 most polluted capital cities in the world. *Environ Pollut* 2020; **266** : 115042.

(3) Chen LA, Chien LC, Li Y, Lin G. Nonuniform impacts of COVID-19 lockdown on air quality over the United States. *Sci Total Environ*2020; **745** : 141105.

(4) Kabir M, Afzal MS, Khan A, Ahmed H. COVID-19 pandemic and economic cost; impact on forcibly displaced people. *Travel Med Infect Dis*2020; **35** : 101661.

(5) Philip RA-O, Purtill H, Reidy E, et al. Unprecedented reduction in births of very low birthweight (VLBW) and extremely low birthweight (ELBW) infants during the COVID-19 lockdown in Ireland: a 'natural experiment' allowing analysis of data from the prior two decades.*BMJ Glob Health* 2020; **5(9)** : e003075.

(6) Pfefferbaum B, North CS. Mental health and the COVID-19 pandemic.*N Engl J Med* 2020; **383(6)** : 510-512.

(7) Sun Y, Hu X, Xie J. Spatial inequalities of COVID-19 mortality rate in relation to socioeconomic and environmental factors across England.*Sci Total Environ* 2021; **758** : 143595.

(8) Kc A, Gurung R, Kinney MV, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. *Lancet Glob Health* 2020; **8(10)** : e1273- e1281.

(9) Li M, Yin H, Jin Z, et al. Impact of Wuhan lockdown on the indications of cesarean delivery and newborn weights during the epidemic period of COVID-19. *PLoS One* 2020; **15(8)** : e0237420.

(10) Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;**7(1)** : e37-e46.

(11). Hedermann G, Hedley PL, Bækvad-Hansen M, et al. Danish premature birth rates during the COVID-19 lockdown. *Arch Dis Child Fetal Neonatal Ed* 2021; **106(1)** : 93-95

(12) Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA* 2020; **324(7)** : 705-706.

(13) Been JV, Burgos Ochoa L, Bertens LCM, Schoenmakers S, Steegers EAP, Reiss IKM. Impact of COVID-19 mitigation measures on the incidence of preterm birth: a national quasi-experimental study. *Lancet Public Health* 2020; **5(11)** : e604- e611.

(14) Caniglia EC, Magosi LE, Zash R, et al. Modest reduction in adverse birth outcomes following the COVID-19 lockdown. *Am J Obstet Gynecol* 2020; S0002-9378(20)32574-6.

(15) Pereira G, Belanger K, Ebisu K, Bell ML. Fine Particulate matter and risk of preterm birth in connecticut in 2000–2006: a longitudinal study. *Am J Epidemiol* 2014; **179(1)** : 67-74.

(16) Zhang Y, Ma Z. Psychological responses and lifestyle changes among pregnant women with respect to the early stages of COVID-19 pandemic.*Int J Soc Psychiatry* 2020; 20764020952116.

(17) Arnaez J, Ochoa-Sangrador C, Caserío S, et al. Lack of changes in preterm delivery and stillbirths during COVID-19 lockdown in a European region. *Eur J Pediatr* 2021; 1-6.

(18) Matheson A, McGannon CJ, Malhotra A, et al. Prematurity rates during the coronavirus disease 2019 (COVID-19) pandemic lockdown in Melbourne, Australia. *Obstet Gynecol* 2021; **137(3):**405-407.

(19) McDonnell S, McNamee E, Lindow SW, O'Connell MP. The impact of the Covid-19 pandemic on maternity services: a review of maternal and neonatal outcomes before, during and after the pandemic. *Eur J Obstet Gynecol Reprod Biol* 2020; **255** : 172-176.

(20) He J, Liu Y, Xia X, et al. Ambient temperature and the risk of preterm birth in Guangzhou, China (2001–2011). *Environ Health Perspect* 2016; **124(7)** : 1100-1106.

(21) Guo T, Wang Y, Zhang H, et al. The association between ambient temperature and the risk of preterm birth in China. *Sci Total Environ* 2018; **613-614** : 439-446.

(22) Ministry of Emergency Management P. National Emergency Response Plan for Public Emergencies. 2006. http://www.gov.cn/gzdt/2006-02/28/content_213129.htm (accessed Feb 25, 2021).

(23) Chang HH, Warren JL, Darrow LA, Reich BJ, Waller LA. Assessment of critical exposure and outcome windows in time-to-event analysis with application to air pollution and preterm birth study.*Biostatistics* 2015; **16(3)** : 509-521.

(24) WHO. Preterm birth.2018. https://www.who.int/news-room/fact-sheets/detail/preterm-birth (accessed Feb 26, 2021).

(25) American College of Obstetricians and Gynecologists and Task Force on Hypertension in Pregnancy. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.*Am J Obstet Gynecol* 2000; **183(1)** : S1-S22.

(26) Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*2010; **33(3)** : 676-682.

(27) Schenker N, Gentleman JF. On judging the significance of differences by examining the overlap between confidence intervals.*The American Statistician* 2001; **55(3)** : 182-186.

(28) Main EK, Chang SC, Carpenter AM, et al. Singleton preterm birth rates for racial and ethnic groups during the coronavirus disease 2019 pandemic in California. *Am J Obstet Gynecol* 2021;**224(2)** : 239-241.

(29) China Daily. Lessons from COVID-19 outbreak. 2020.*https://www.chinadaily.com.cn/a/202002/17/WS5e4a077ba310128* Mar 8, 2021).

(30) Corbett GA, Milne SJ, Hehir MP, Lindow SW, O'Connell MP. Health anxiety and behavioural changes of pregnant women during the COVID-19 pandemic. *Eur J Obstet Gynecol Reprod Biol* 2020; **249** : 96-97.

(31) WHO. Maternal mental health. 2019. https://www.who.int/teams/mental-health-and-substance-use/maternal-mental-health (accessed Mar 2, 2021).

(32) Thapa SB, Mainali A, Schwank SE, Acharya G. Maternal mental health in the time of the COVID-19 pandemic. *Acta Obstet Gynecol Scand*2020; **99(7)** : 817-818.

(33) Fisher J, Cabral de Mello M, Patel V, et al. Prevalence and determinants of common perinatal mental disorders in women in low- and lower-middle-income countries: a systematic review. *Bull World Health Organ* 2012; **90(2)** : 139G-149G.

(34) Ministry of culture and tourism of the People's Republic of China. Novel coronavirus pneumonia epidemic prevention and control work has been actively deployed in various province. 2020. https://www.mct.gov.cn/whzx/whyw/202001/t20200126_850573.htm (accessed Mar 8, 2020).

(35) López-Morales H, Del Valle MV, Canet-Juric L, et al. Mental health of pregnant women during the COVID-19 pandemic: A longitudinal study.*Psychiatry Res* 2021; **295** : 113567.

(36) Sidor A, Rzymski P. Dietary choices and habits during COVID-19 lockdown: experience from Poland. *Nutrients* 2020; **12(6)** : 1657.

(37) Langley-Evans SC. Nutrition in early life and the programming of adult disease: a review. *J Hum Nutr Diet* 2015; **28(Suppl 1)** :1-14.

(38) van de Loo KFE, Vlenterie R, Nikkels SJ, et al. Depression and anxiety during pregnancy: the influence of maternal characteristics.*Birth* 2018; **45(4)** : 478-489.

(39) Madzorera I, Isanaka S, Wang M, et al. Maternal dietary diversity and dietary quality scores in relation to adverse birth outcomes in Tanzanian women. *Am J Clin Nutr* 2020; **112(3)** : 695-706.

(40) Fatima M, Srivastav S, Mondal AC. Prenatal stress and depression associated neuronal development in neonates. I*nt J Dev Neurosci*2017; **60** : 1-7.

(41) Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): a review. *Int J Surg* 2020; **78** : 185-193.

(42) Lian X, Huang J, Huang R, Liu C, Wang L, Zhang T. Impact of city lockdown on the air quality of COVID-19-hit of Wuhan city. *Sci Total Environ* 2020; **742** : 140556.

(43) Li J, Yang J. Risk and Imbalance: A narrative analysis of daily life of marriage and divorce among urban youth during the COVID-19 epidemic. *The Journal of Humanities* 2020; **10** : 13-19. (in Chinese).

(44) Matei A, Saccone G, Vogel JP, Armson AB. Primary and secondary prevention of preterm birth: a review of systematic reviews and ongoing randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol*2019; **236** : 224-239.

(45) Koullali B, Oudijk MA, Nijman TAJ, Mol BWJ, Pajkrt E. Risk assessment and management to prevent preterm birth. *Semin Fetal Neonatal Med* 2016; **21(2)** : 80-88.

Table 1 General characteristics of study participants

	Unexposed group (n=493,496) No. of participants (%)	**Exposed group (n=101,900) No. of participants0** (%)	χ^2	P
Maternal age (years)				
<24	50255 (10.2)	8412 (8.3)	660.24	<0.001
24–26	81222 (16.5)	15864 (15.6)		
27–29	118040 (23.9)	23723 (23.3)		
30–32	102817 (20.8)	23585 (23.1)		
33–35	72330 (14.7)	16094 (15.8)		
>35	68832 (13.9)	14222 (13.9)		
Residential city				
Guangzhou	19850 (4.0)	2970 (2.9)	1193.80	<0.001
Dongguan	34579 (7.0)	5641 (5.5)		
Jiangmen	18107 (3.7)	3303 (3.3)		
Shenzhen	75334 (15.3)	13280 (13.0)		
Foshan	345626 (70.0)	76706 (75.3)		
Infant sex			<0.01	0.950
Male	263153 (53.3)	54349 (53.3)		
Female	230343 (46.7)	47551 (46.7)		
Pregnancy complications (N=173064)*				
Hypertensive disorders of pregnancy (HDP)			96.57	<0.001
No	143933 (97.3)	24369 (96.7)		
Yes	3937 (2.7)	825 (2.3)		
Gestational hypertension	971 (0.7)	252 (1.0)		
Pre-eclampsia / Eclampsia	2712 (1.8)	473 (1.9)		

	Unexposed group (n=493,496) No. of participants (%)	**Exposed group (n=101,900) No. of participants0 (%)**	χ^2	P
Chronic hypertension	141 (0.1)	44 (0.2)		
Chronic hypertension with superimposed pre-eclampsia	113 (0.1)	56 (0.2)		
Gestational diabetes mellitus (GDM)			183.64	<0.001
No	129653 (87.7)	21313 (84.6)		
Yes	18217 (12.3)	3881 (15.4)		
Preterm birth			15.58	<0.001
No	467865 (94.8)	96307 (94.5)		
Yes	25631 (5.2)	5593 (5.5)		
Very premature (<32 GWs)	2121 (0.4)	443 (0.4)		
Moderate/late premature (32-36 GWs)	23510 (4.8)	5150 (5.1)		
Stillbirth (N=595904)			3.36	0.067
No	493496 (99.92)	101900 (99.90)		
Yes	405 (0.08)	103 (0.10)		
Marital status			472.03	<0.001
Married	488376 (99.0)	100631 (98.8)		
Unmarried	4263 (0.8)	732 (0.7)		
Other	857 (0.2)	537 (0.5)		
Parity			2121.60	<0.001
0 (Primiparas)	415074 (84.1)	79686 (78.2)		
1 (Multiparas)	63158 (12.8)	17603 (17.3)		
2-4 (Multiparas)	15264 (3.1)	4611 (4.5)		
Delivery type			1871.40	<0.001
Natural delivery	297591 (60.3)	63394 (62.2)		
Operative vaginal delivery	16735 (3.4)	1055 (1.0)		
Cesarean delivery	179027 (36.3)	37298 (36.6)		
Other	143 (<0.1)	153 (0.2)		
	Mean±SD	**Mean±SD**	t	P
Maternal age (years)	29.78±5.09	30.07±4.94	17.11	<0.001
Gestational length (week Mean ± SD)	38.74±1.46	38.66±1.46	16.22	<0.001

* Data that were not available in hospitals in Foshan, because the information were not recorded in the birth certification system.

Table 2. Associations of exposure to the COVID-19 lockdown with gestational length

	No. of participants	No. of participants	Gestational length (week, Mean±SD)	Gestational length (week, Mean±SD)	Mean difference in gestational length (week)	Mean difference in gestational length (week)
	Unexposed group	**Exposed group** [b]	**Unexposed group**	**Exposed group** [b]	**Crude β (95% CI)**	**Adjusted β (95% CI)** [*]
Gestational week at the beginning of the Level I lockdown						
All	493496	101900	38.74±1.46	38.66±1.46	-0.08 (-0.09, -0.07)	-0.06 (-0.07, -0.05)
Conception during the lockdown	64645	11317	38.72±1.52	38.64±1.49	-0.08 (-0.11, -0.05)	-0.04 (-0.07, -0.01)
Prior to 4th	53300	10937	38.71±1.50	38.64±1.50	-0.07 (-0.10, -0.04)	-0.10 (-0.14, -0.07)
4th -7th	50973	10494	38.67±1.52	38.52±1.54	-0.14 (-0.17, -0.11)	-0.13 (-0.16, -0.09)
8th -11th	48926	10237	38.70±1.50	38.58±1.54	-0.12 (-0.15, -0.08)	-0.10 (-0.13, -0.07)
12th -15th	46255	9844	38.73±1.51	38.61±1.55	-0.11 (-0.15, -0.08)	-0.11 (-0.14, -0.07)
16th -19th	45913	9539	38.74±1.48	38.63±1.52	-0.11 (-0.14, -0.08)	-0.10 (-0.13, -0.06)
20th -23rd	41017	8830	38.74±1.49	38.64±1.52	-0.10 (-0.14, -0.07)	-0.10 (-0.13, -0.06)
24th -27th	40358	8750	38.68±1.49	38.66±1.44	-0.02 (-0.06, 0.01)	-0.01 (-0.04, 0.03)
28th -31st	38146	8101	38.72±1.39	38.63±1.36	-0.09 (-0.12, -0.06)	-0.07 (-0.10, -0.04)
32nd -36th	47382	10213	38.74±1.21	38.73±1.18	-0.01 (-0.03, 0.02)	0.02 (-0.01, 0.04)
37th - 41st	16581	3638	39.40±0.92	39.41±0.93	0.01 (-0.02, 0.04)	0.03 (0.01, 0.07)
	Exposure dose (Mean±SD)	**Exposure dose (Mean±SD)**	**Gestational length (week, Mean±SD)**	**Gestational length (week, Mean±SD)**	**Mean difference in gestational length (week)**	**Mean difference in gestational length (week)**

	No. of participants	No. of participants	Gestational length (week, Mean±SD)	Gestational length (week, Mean±SD)	Mean difference in gestational length (week)	Mean difference in gestational length (week)
	Unexposed group	**Exposed group**	**Unexposed group**	**Exposed group**	**Crude β (95% CI)**	**Adjusted β (95% CI)** [*]
Cumulative exposure dose in the first 22 weeks during the Level I to the Level III lockdown [a]						
Per 100 unit increase in all participants	0±0	195.08±82.21	38.74±1.45	38.61±1.52	-0.06 (-0.07, -0.05)	-0.05 (-0.06, -0.04)
Categories of cumulative exposure dose						
Unexposed group	0±0	-	38.74±1.45	-	Reference	Reference
Q_1 (<132)	-	73.40±38.11	-	38.64±1.52	-0.10 (-0.13, -0.08)	-0.09 (-0.11, -0.07)
Q_2 (132-225)	-	178.66±27.17	-	38.59±1.54	-0.15 (-0.17, -0.12)	-0.13 (-0.16, -0.11)
Q_3 (226-263)	-	247.18±10.58	-	38.58±1.51	-0.16 (-0.18, -0.13)	-0.14 (-0.16, -0.11)
Q_4 ([?]264)	-	278.80±8.59	-	38.62±1.51	-0.12 (-0.14, -0.10)[*]	-0.09 (-0.11, -0.07)
P for trend test						< 0.001

Adjusted for maternal age, marital status, parity, residential city, delivery type and infant sex.

In calculating the cumulative exposure dose to lockdown, we assigned a weighting of 3 to days with Level I response, 2 to days with Level II response, 1 to days with Level III response, and 0 to other days.

a: The exposed group refers to the pregnant women who have experienced the COVID-19 lockdown in their first 22 GWs. The other participants were defined as the unexposed group. The individual cumulative exposure dose was calculated by combining the weightings with the overlap between their pregnancy period [?]22 GWs and the three levels of responses. Q1-Q4 were defined as the cumulative exposure dose of the exposed group classified by quartiles, and the unexposed group was used as reference.

b: Pregnant women who have experienced the COVID-19 lockdown (from 1/23/2020 to 2/24/2020) during any period of their pregnancy were defined as the exposed group. We further divided the exposed group into subgroups according to their gestational weeks (GW) on 1/23/2020, the beginning of lockdown. -: Not applicable.

Table 3. Associations of exposure to the COVID-19 lockdown with preterm birth

	Unexposed group (n
	Term birth
Gestational week at the beginning of the Level I lockdown	
All	451284 (94.7)
Conception during the lockdown	61117 (94.5)
Prior to 4th	50272 (94.3)
4th -7th	48023 (94.3)
8th -11th	46128 (94.3)
12th -15th	43652 (94.4)
16th -19th	43439 (94.6)
20th -23rd	38806 (94.6)
24th -27th	38052 (94.3)
28th -31st	36145 (94.8)
32nd -36th	45650 (96.3)
	Exposure dose in un
Cumulative exposure dose in the first 22 weeks during Level I to Level 3 lockdown [b]	
Per 100unit increase	0±0
Categories of cumulative exposure dose	
Unexposed group	0±0
Q_1 (<132)	-
Q_2 (132-225)	-
Q_3 (226-263)	-
Q_4 ([?]264)	-
P for trend test	

*: Adjusted for maternal age, marital status, parity, residential city, delivery type and infant sex. PTB: preterm birth; MPTB: moderate preterm birth; VPTB: very preterm birth N/A: There is no VPTB case in the subgroup.

a: Pregnant women who have experienced the COVID-19 lockdown (from 1/23/2020 to 2/24/2020) during any period of their pregnancy were defined as the exposed group. We further divided the exposed group into subgroups. according to their gestational weeks (GW) on 1/23/2020, the beginning of lockdown. In calculating the cumulative exposure dose to lockdown, we assigned a weighting of 3 to days with Level I response, 2 to days with Level II response, 1 to days with Level III response, and 0 to other days.

b: The exposed group refers to the pregnant women who have experienced the COVID-19 lockdown in their first 22 GWs. The rest of included participants were defined as the unexposed group. The individual cumulative exposure dose was calculated by combining the weightings with the overlap between their pregnancy period [?]22 GWs and the three levels of responses. Q_1-Q_4 were defined as the cumulative exposure dose of the exposed group classified by quartiles, and the unexposed group were used as reference. -: Not applicable

Table 4. Modification effects of infant sex on the associations of COVID-19 lockdown exposure with gestational length and PTB risk

	No. of participants	No. of participants	No. of participants	No. of participants	Gestational length (week, Mean±SD)	Gestational length (week, Mean±SD)	Gestational length (week, Mean±SD)	Gestational length (week, Mean±SD)	Mean difference in gestational length (week) Adjusted β (95% CI) *	Mean difference in gestational length (week) Adjusted β (95% CI) *
	Male Unexposed group	Male Exposed group [a]	Female Unexposed group	Female Exposed group [a]	Male Unexposed group	Male Exposed group [a]	Female Unexposed group	Female Exposed group [a]	Male	Female
Gestational week during the Level I lockdown										
All	263153	54349	230343	47551	38.66±1.48	38.58±1.48	38.82±1.43	38.74±1.44	-0.06 (-0.08, -0.05)	-0.06 (-0.08, -0.05)
	No. of participants	**No. of participants**	**No. of participants**	**No. of participants**	**PTB rate (N, %)**	**PTB rate (N, %)**	**PTB rate (N, %)**	**PTB rate (N, %)**	**PTB risk Adjusted OR (95%CI) ***	**PTB risk Adjusted OR (95%CI) ***
	Male Unexposed group	Male Exposed group [a]	Female Unexposed group	Female Exposed group [a]	Male Unexposed group	Male Exposed group [a]	Female Unexposed group	Female Exposed group [a]	Male	Female
Gestational week during the Level I lockdown										
All	254522	52471	222393	45791	14873 (5.8)	3269 (6.2)	10758 (4.8)	2324 (5.1)	1.09 (1.04, 1.13)	1.08 (1.03, 1.13)

*: Adjusted for maternal age, marital status, residential city, delivery type and parity.

PTB: preterm birth

a: Pregnant women who have experienced the COVID-19 lockdown (from 1/23/2020 to 2/24/2020) during their any period of pregnancy were defined as the exposed group.

Figure legends

Figure 1. Geographic locations of the 5 study cities in Guangdong Province, South China

Figure 2. Approach to calculating individual cumulative exposure dose to lockdown in the first 22 GWs

: Weeks after 22 GWs.

Note: A, B, C, D and E represent subgroups of pregnant women with different GWs during the Level I lockdown; We assigned a weighting value of 3 to the days with Level I response, 2 to the days with Level II response, 1 to the days with Level III response, and 0 to days before lockdown (no exposure).

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