BMJ Open

Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047900
Article Type:	Original research
Date Submitted by the Author:	12-Dec-2020
Complete List of Authors:	Du, Min; Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China Yang, Jie; Maternal and Child Health Hospital of Tongzhou District, Beijing, China. Han, Na; Maternal and Child Health Hospital of Tongzhou District, Beijing, China. Liu, Min ; Peking University, School of Public Health, Department of Epidemiology & Biostatistics Liu, Jue; Peking University School of Public Health, Department of Epidemiology & Biostatistics
Keywords:	COVID-19, Public health < INFECTIOUS DISEASES, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title: Association between COVID-19 pandemic and the risk of adverse pregnancy outcomes: a cohort study

Authors: Min Du[1*], Jie Yang[2*], Na Han[2], Min Liu[1], Jue Liu[1,3]

[*]Contributed equally.

Running title: COVID-19 pandemic and pregnancy outcome

Affiliations:

[1] Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China

[2] Maternal and Child Health Hospital of Tongzhou District, Beijing, China

[3] National Health Commission Key Laboratory of Reproductive Health, Peking University Health Science Center

Address correspondence to: Dr. Jue Liu, Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China.

E-mail address: jueliu@bjmu.edu.cn

Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

ABSTRACT

Objectives The secondary impacts of the COVID-19 pandemic on adverse maternal and neonatal outcomes remain unclear. In this study, we aimed to evaluate the association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes.

Design We conduced retrospective analyses on 2 cohorts comprising 7699 pregnant women in Beijing, China, and compared pregnancy outcomes between the pre-COVID-2019 cohort (women who delivered from May 20, 2019 to November 30, 2019) and the COVID-2019 cohort (women who delivered from January 20, 2020 to July 31, 2020). The secondary impacts of the COVID-2019 pandemic on pregnancy outcomes were assessed by using multivariate log-binomial regression models, and we used interrupted time-series regression (ITS) analysis to further control the effects of time-trends.

Setting One tertiary-level centre in Beijing, China

Participants 7699 pregnant women.

Results Compared with women in the pre-COVID-19 pandemic group, pregnant women during the COVID-2019 pandemic were more likely to be of advanced age, exhibit insufficient or excessive gestational weight gain, and show a family history of chronic disease (all $P<0.05$). After controlling for other confounding factors, the risk of premature rupture of membranes and foetal distress was increased by 11% (95% CI, 1.04, 1.18; $p < 0.01$) and 14% (95% CI, 1.01, 1.29; $p < 0.05$), respectively, during the COVID-2019 pandemic. The association still remained in the ITS analysis after additionally controlling for time-trends (all $P<0.01$). We uncovered no other associations between the COVID-19 pandemic and other pregnancy outcomes ($P >0.05$).

Conclusions During the COVID-19 pandemic, more women manifested either insufficient or excessive gestational weight gain; and the risk of premature rupture of membranes and foetal distress was also higher during the pandemic.

Keywords: COVID-19, pregnancy outcome, cohort study

Strengths and limitations of this study

A major strength of this study was our estimation of the secondary impacts of the COVID-19 pandemic on adverse maternal and neonatal outcomes in China, the first such study of its kind.

We collected materials from the hospital-information system, which assured the accuracy of our data.

This study was of a retrospective nature and thus did not include physical exercise, diet, or psychological status, which might also be related to pregnancy outcomes.

The follow-up period in this study was only until delivery, such that the long-term impacts of the COVID-19 pandemic on women and their infants could not be explored.

Larger and multi-centre prospective cohort studies are needed to confirm and to clarify the findings of our study.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has developed into the largest and deadliest pandemic respiratory disease. As of August 23, 2020, a total of 23,057,288 cases and 800,906 deaths have been reported to the World Health Organization (WHO). Perinatal research on COVID-19 is now primarily focused on pregnancy outcomes of women infected with SARS-CoV-2—including caesarean section[1,2], foetal distress[1], preterm birth[3], and even maternal death[4]. However, the adverse secondary impacts of the COVID-19 pandemic on maternal and neonatal outcomes remain unknown.

Several investigators have explored the effects of the COVID-19 pandemic on the mental health of pregnant women[5-8]. Ahorsu et al. found that the fear of COVID-19 was associated with depression, suicidal intention, adverse mental-health effects, and diminished overall quality of life among pregnant women[5]. Some studies showed that the COVID-19 pandemic was associated with obstetric care[9-12]—including institutional deliveries, high-risk pregnancy[9], intrapartum foetal heart rate monitoring, breastfeeding within 1 h of birth[10], and prenatal diagnosis/screening tests; while others have shown an effect of the pandemic on causing adverse maternal and neonatal outcomes[9,10,13-15]. The COVID-19 pandemic was associated with higher percentages of gestational

hypertension[13,14], gestational diabetes[14], and premature rupture of membranes[15]. Goyal et al. reported that there was an increased rate of admission to the intensive care unit for pregnant women during the pandemic, compared with prior to COVID-19[9]. Ashish et al. also found that both the rate of institutional stillbirth and institutional neonatal mortality increased significantly during the lockdown period in Nepal[10].

However, a majority of investigators [9,10,13-15] have only compared the rate of adverse maternal and neonatal outcomes between the pre-COVID-19 period and the COVID-19 pandemic period without controlling important factors related to adverse pregnancy outcomes (e.g., parity, gestational weight gain, or a family history of chronic disease). Thus, it is evident that more research is needed regarding the effects of the pandemic on some specific adverse outcomes, including caesarean section, foetal distress, low birth weight, and macrosomia. Unfortunately, in none of the previously aforementioned studies was there an examination of the association between the COVID-19 pandemic and adverse pregnancy outcomes in mainland China.

Therefore, we aimed in the present study to evaluate the secondary impacts of the COVID-19 pandemic on the risk of adverse pregnancy outcomes, using two cohorts (a pre-COVID-19 cohort and a COVID-19 cohort) to provide evidence for the implementation of targeted strategies that promote maternal and infant health during the COVID-19 pandemic.

METHODS

Study population

Two retrospective cohorts (pre-COVID-19 and during COVID-19) were analysed in this study, using the following inclusion criteria: (1) women with singleton pregnancies, (2) pregnant women who made prenatal visits to the Maternal and Child Health Hospital of Tongzhou District in Beijing, and (3) women who delivered between 2019 and July 31, 2020.

There were 8324 pregnant women who gave birth between January 1, 2019 and December 31, 2019; and 3532 pregnant women who gave birth between January 1, 2020 and July 31, 2020. Although we herein focused on the overall effects of the COVID-19 pandemic, none of the participants was infected with SARS-CoV-2 (the virus that causes *COVID-19*), given that the first case in China was reported in December 2019 and the first case in Beijing was reported in

January 2020. To better assess the influence of the COVID-19 pandemic locally, we excluded the 613 participants who delivered during December 2019; the 344 women who delivered between January 1, 2020 and January 19, 2020; and also the 3202 pregnant women who delivered between January 1, 2019 and May 19, 2019. Because we decided to only make close temporal comparisons in order to avoid certain potentially confounding factors (e.g., differing policies between 2019 and 2020), we chose women who delivered from May 20, 2019 to November 30, 2019 as the pre-COVID-19 cohort; and those who delivered from January 20, 2020 to July 31, 2020 as the COVID-19 cohort. We thus included 4511 pregnant women in the pre-COVID-19 cohort and 3188 pregnant women in the COVID-19 cohort. However, in order to estimate the effects of the COVID-19 pandemic on other pregnancy outcomes (e.g., preterm birth and low birth weight), we excluded two stillbirth in the pre-COVID-19 cohort and three stillbirths in the COVID-19 cohort. We therefore ultimately included 4509 pregnant women who gave birth prior to the COVID-19 pandemic and 3185 pregnant women who gave birth during the COVID-19 pandemic (supplemental Figure 1). This study was approved by the Institutional Review Boards at Peking University (IRB00001052-18003).

Data collection

Data were collected from the hospital-information system, including basic demographic characteristics (age, ethnicity, occupation, and education), pregnancy status (gravidity, parity, history of miscarriage, and history of induced abortion), health status (pre-pregnancy body mass index [BMI]), gestational weight gain, a family history of chronic disease, and the number of prenatal visits. Of these characteristics, pre-pregnancy BMI was categorized based on the WHO cut-off points; gestational weight gain was calculated as the difference between weight at the last routine pregnancy visit and the pre-pregnancy weight; and the rate of gestational weight gain was calculated as the gestational weight gain/the gestational weeks at the last routine pregnancy visit. Categorization was in accordance with IOM criteria: gestational weight gain was classified as insufficient, appropriate, or excessive[16]; and a family history of chronic disease was principally with respect to whether the maternal parents or maternal grandparents manifested cardiovascular diseases such as heart disease and diabetes. The number of prenatal visits was not fewer than 8 times per year as recommended by the WHO[17].

Assessment of pregnancy outcomes

For this study we obtained information on pregnancy outcomes according to the ICD codes of discharge diagnosis, including gestational hypertension, gestational diabetes (GDM), premature rupture of membranes, delivery mode, stillbirth, foetal distress, preterm birth, low birth weight, and macrosomia. Preterm birth was defined as less than 37 weeks of gestation based on the interval between the last menstrual period and the date of delivery of the baby. Delivery mode was categorized as either caesarean section or vaginal delivery. Caesarean section included both medical and psychosocial indications, and vaginal delivery included spontaneous vaginal and assisted vaginal births. Infant birth weight was divided into low birth weight (< 2500 g) and macrosomia (> 4000 g).

Statistical analyses

We compared the characteristics of women before and during the COVID-19 pandemic by using the χ^2 or *t* test. The χ^2 test was also used to compare pregnancy outcomes of women before and during the pandemic. Given that odds ratios (ORs) cannot provide accurate estimates for the relative risks (RRs) in the cohort studies, we used univariate and multivariate log-binomial regression models to estimate the crude risk ratios (cRRs) and adjusted risk ratios (aRRs) of the impacts of the COVID-19 pandemic on adverse pregnancy outcomes using the SAS Software Package V.9.4, (SAS Institute). We also calculated the attributable risk percentage (AR%, 95% CI). We performed sensitivity analysis by fitting different models to examine the robustness of the estimation, and 3 models were fitted. The first (model A) was unadjusted; the second (model B) was adjusted for baseline demographic characteristics (maternal age, ethnicity, occupation, education); and the third model (full-model C) was further adjusted for pregnancy condition (gravidity, parity, history of miscarriage, history of induced abortion) and health status (pre-pregnancy BMI, gestational weight gain [GWG], family history of chronic disease, and the number of prenatal visits). We additionally added a full-model C by replacing categorical variables with continuous variables, including maternal age, gravidity, parity, history of miscarriage, history of induced abortion, pre-pregnancy BMI, the rate of gestational weight gain, and the number of prenatal visits. Since interrupted time-series regression (ITS) analysis is useful for evaluating population-level health interventions with a clearly defined point in time [18], we

conducted ITS to examine the impacts of COVID-19 on pregnancy outcomes using R 3.4.2 (R-team)[18]. A 2-sided value of P<0.05 was considered to be statistically significant for all of the analyses.

RESULTS

A total of 7699 women were included in this study, with a mean age of 30.07 (±3.98, SD) and an average gestational week of 38.90 (± 1.46) weeks; 93.87% were of Han ethnicity, 11.83% were unemployed, and 56.97% had a bachelor's degree or less. Characteristics of the study population are provided in **Table 1**. Compared with women in the pre-COVID-19 pandemic group, pregnant women during the COVID-19 pandemic were more likely to be of advanced age (15.53% vs. 13.30%, respectively), show insufficient (28.58% vs. 26.69%) or excessive gestational weight gain (32.21% vs. 31.32%), have a family history of chronic disease (14.18% vs 10.74%), and have ≥8 prenatal visits (9.50% vs. 11.55%, respectively; all *P*<0.05). Other characteristics were not significantly different between the two groups (all *P*>0.05).

The prevalences of caesarean sections and premature rupture of membranes were higher during the COVID-19 pandemic period compared with women prior to the pandemic (48.16% vs. 45.80%, *P*=0.040; and 33.59% vs. 30.72%, respectively; *P*=0.008). However, the prevalences of other pregnancy outcomes were not significantly different during the COVID-19 pandemic compared with the pre-pandemic period (*P*>0.05, **Table 2**).

In our log-binomial regression models, and after adjusting for all confounding factors, the risk for premature rupture of membranes and foetal distress during the COVID-19 pandemic compared to pre-COVID-19 women was increased by 11% (95% CI, 1.04, 1.18; p < 0.01) and 14% (95% CI, 1.01, 1.29; p < 0.05), respectively (**Table 3**). Additionally, the attributable risk percentage of the COVID-19 pandemic on premature rupture of membranes was 9.91 (95% CI, 3.84, 15.25), and the attributable risk percentage of the pandemic on foetal distress was 12.28 (95% CI, 0.99, 22.48). However, we uncovered no other associations between the COVID-19 pandemic and other pregnancy outcomes, and demonstrated similar results for the additional full-model C (as shown in supplemental table 2). After controlling for time-trends in the interrupted time-series regression, the COVID-19 pandemic was still associated with an increased risk of premature

rupture of membranes (*P*<0.001, Figure **1**) and foetal distress (*P*<0.01, Figure **2**).

DISCUSSION

To the best of our knowledge, this is the first cohort study to focus on secondary impacts of the COVID-19 pandemic on pregnancy outcomes in mainland China. Herein, we showed **that** more pregnant women were of advanced age, with abnormal gestational weight gain, and a family history of chronic disease during the COVID-19 pandemic. The risks of premature rupture of membranes and foetal distress among pregnant women who gave birth during the COVID-19 pandemic were also higher than in those women who gave birth before the pandemic.

Although researchers had previously found that the prevalence of premature rupture of membranes in pregnant women infected with the novel coronavirus was relatively high[2,19-21], few had explored the secondary impacts of the COVID-19 pandemic on this adverse pregnancy outcome. Kugelman et al. found that there was a higher proportion of women who had premature rupture of membranes in a COVID-19 cohort (20.6% vs. 11.0%, p<0.001)[15]; and in the present study, we also found that the proportion of women who presented with premature rupture of membranes was higher in the COVID-19 cohort (33.59% vs. 30.72%, *P*=0.008). Compared to women pre-COVID-19, we observed that the risk of premature rupture of membranes during the COVID-19 pandemic was increased by 11% (95% CI, 1.04, 1.18; p < 0.01). Premature rupture of membranes may additionally be associated with increased maternal anxiety during the COVID-19 pandemic[6,7]. Studies have shown that as the severity of the pandemic increased, the level of anxiety among pregnant women also increased[22]; and that maternal anxiety and depression were associated with premature rupture of membranes [23]because of the decreased levels of creatine and choline[24] and an altered diurnal pattern of cortisol (manifested as a flattened cortisol decline and higher evening cortisol) [25,26]. We also found that the risk of foetal distress was increased during the pandemic, but noted a general lack of published research on this topic. The association might be related to enhanced psychological, neuroendocrine, and neurochemical changes caused by social-isolation stress during the COVID-19 pandemic[27]. Many countries took measures to control the transmission of the virus by keeping social distance (e.g., stay-at-home orders, the cancellation of public events, lockdown),

which may increase the risk of social-isolation stress for pregnant women[27]. In one study, it was reported that one-third of women underwent an inadequate number of antenatal visits because of the lockdown for fear of contracting infection, resulting in 44.7% of pregnancies showing complications[9]. In addition, women pregnant during the COVID-19 pandemic might not have visited the hospital as frequently as in a non-pandemic time, which might have led to under instruction in perinatal healthcare and inadequate receipt of routine medical services [28]. However, the specific mechanism(s) underlying the effects on pregnancy of the COVID-19 pandemic remains unclear. In order to reduce the impact of COVID-19 pandemic on psychological health and increase the usage of perinatal healthcare for pregnant women during the pandemic, the National Health Commission of China launched a new notice on February 8, 2020 that proposed strengthening health counselling, screening, and follow-ups for pregnant women[29]. Besides, local hospital had tried their best to ensure the access to prenatal care by taking comprehensive measures (e.g., online appointment service, online consultation work, outpatient service and so on) to minimize the influence of COVID-19 pandemic on pregnancy and medical services. Nevertheless, our study showed that the secondary impacts of COVID-19 on pregnant women should draw greater attention, especially with respect to the premature rupture of membranes and foetal distress.

In our study, the prevalence of caesarean sections among pregnant women experiencing the COVID-19-pandemic was higher than in the group prior to the pandemic, which may be related to the higher proportions of caesarean-section indices that included foetal distress. We also found that there was a greater proportion of women aged ≥35 years in the COVID-19 cohort, and that this cohort contained more women with a family history of chronic disease. Kugelman et al. additionally found that women visited the obstetrical emergency department at a more advanced mean gestational age during the pandemic outbreak, compared with the pre-COVID period [15]. We surmised that this may be related to the 2-child policy implemented in January of 2016 in China. Zhao et al. found that the percentages of older pregnant women increased significantly in 2017 and 2018 compared with numbers in 2014, 2015 and 2016[30]. These results suggest that attention should be paid to the health status of pregnant women, especially those women of advanced reproductive age and with a family history of chronic diseases. Pregnant

women who visit outpatient clinics should also be followed as often as possible, and the psychological and emotional states of these women should be assessed and monitored in follow-up visits to address the possible risks of adverse pregnancy complications and outcomes[31].

The strengths of this study included its cohort-study design and use of well-established methods to detect the impacts of the COVID-19 pandemic on pregnancy outcomes, and we thus included two cohorts (a pre-COVID-19 cohort and a COVID-19 cohort), using the same study site. In addition, using log-binomial regression models and interrupted time-series analysis, we were able to evaluate the impact of a policy change or natural intervention (such as a pandemic).

There were some limitations to our study. First, this study was a retrospective study. We did not collect data on physical exercise, diet, or psychological status, which might also be related to pregnancy outcomes. The follow-up period for this study was only up to delivery, such that long-term impacts of the COVID-19 pandemic on women and their infants could not be explored. Second, this is a single-centre cohort study, and we only included participants at 1 hospital in Beijing. Therefore, these results may have limited relevance to other health-care systems outside of Beijing. Larger and multi-centre prospective cohort studies are therefore needed in the future to confirm and clarify the findings of our study. Finally, due to the lack of specific individual obstetric-management records, we could not investigate the impacts of specific measures on pregnancy outcomes.

In summary, in the present study, we demonstrated that there were more pregnant women of an advanced age, with abnormal gestational weight gain, and with a family history of chronic disease during the COVID-19 pandemic. The risk for premature rupture of membranes and foetal distress in pregnant women during the pandemic was also higher than in pregnant women before the COVID-19 pandemic. Our findings highlight the importance of improved management during pregnancy to reduce adverse maternal and infant outcomes, especially with respect to premature rupture of membranes and foetal distress. However, larger and multi-center cohort studies are needed to confirm and clarify our findings.

Contributors

All the authors have made substantial contributions to the conception, design of the work; or the acquisition, analysis, or interpretation of data for the work. They have participated in drafting the manuscript and approval of the version to be published. Conceptualization: Jue Liu. Methodology: Jue Liu, Min Liu. Investigation: Min Du, Jie Yang, Jue Liu. Data acquisition: Jie Yang, Na Han. Data Curation: Min Du, Jie Yang, Jue Liu. Data analysis: Min Du, Jie Yang. Preparation of tables and figures: Min Du. Initial draft of manuscript: Min Du, Jie Yang, Jue Liu. Writing – Review & Editing: Na Han, Min Liu, Jue Liu. Supervision: Jue Liu.

Funding

This research was funded by the National Natural Science Foundation of China (grant number 81703240) and the National Key Research and Development Project of China (grant number 2020YFC0846300).

Competing interests

All authors report no conflict of interest.

Patient consent for publication Not required

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request to the corresponding author.

Ethics approval This study was approved by the Institutional Review Boards at Peking University (IRB00001052-18003).

REFERENCE

1 Gao YJ, Ye L, Zhang JS, et al. Clinical features and outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2020;20:564.

2 Zhang L, Dong L, Ming L, et al. Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection during late pregnancy: a report of 18 patients from Wuhan, China. BMC Pregnancy Childbirth. 2020;20:394.

3 Lokken EM, Walker CL, Delaney S, et al. Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington State [published online ahead of print, 2020 May 19]. Am J Obstet Gynecol. 2020;S0002-9378(20)30558-5.

4 Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. Am J Obstet Gynecol. 2020;223:109.e1-109.e16.

5 Ahorsu DK, Imani V, Lin CY, et al. Associations Between Fear of COVID-19, Mental Health, and Preventive Behaviours Across Pregnant Women and Husbands: An Actor-Partner Interdependence Modelling [published online ahead of print, 2020 Jun 11]. Int J Ment Health Addict. 2020;1-15. doi:10.1007/s11469-020-00340-x6.

6 Berthelot N, Lemieux R, Garon-Bissonnette J, et al. Uptrend in distress and psychiatric symptomatology in pregnant women during the coronavirus disease 2019 pandemic. Acta Obstet Gynecol Scand. 2020;99:848-855.

7 Hessami K, Romanelli C, Chiurazzi M, Cozzolino M. COVID-19 pandemic and maternal mental health: a systematic review and meta-analysis [published online ahead of print, 2020 Nov 1]. J Matern Fetal Neonatal Med. 2020;1-8. doi:10.1080/14767058.2020.1843155

8 Lemieux R, Garon-Bissonnette J, Loiselle M, Martel É, Drouin-Maziade C, Berthelot N. Association entre la fréquence de consultation des médias d'information et la détresse psychologique chez les femmes enceintes durant la pandémie de COVID-19: Association between news media consulting frequency and psychological distress in pregnant women during the COVID-19 pandemic [published online ahead of print, 2020 Oct 21]. Can J Psychiatry. 2020;706743720963917. doi:10.1177/0706743720963917

9 Goyal M, Singh P, Singh K, Shekhar S, Agrawal N, Misra S. The effect of the COVID-19 pandemic on maternal health due to delay in seeking health care: Experience from a tertiary center [published online ahead of print, 2020 Oct 31]. Int J Gynaecol Obstet. 2020;10.1002/ijgo.13457. doi:10.1002/ijgo.13457

10 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. doi:10.1016/S2214-109X(20)30345-4

11 Lalaguna Mallada P, Díaz-Gómez NM, Costa Romero M, San Feliciano Martín L, Gabarrell Guiu C. Impacto de la pandemia de Covid-19 en la lactancia y cuidados al nacimiento. Importancia de recuperar las buenas prácticas [The impact of Covid-19 pandemic on breastfeeding and birth care. The importance of recovering good practices.]. Rev Esp Salud Publica. 2020;94:e202007083. Published 2020 Jul 9.12.

12 Ozalp M, Demir O, Akbas H, Kaya E, Celik C, Osmanagaoglu MA. Effect of COVID-19 pandemic process on prenatal diagnostic procedures [published online ahead of print, 2020 Sep 1]. J Matern Fetal Neonatal Med. 2020;1-6. doi:10.1080/14767058.2020.1815190

13 Gu XX, Chen K, Yu H, Liang GY, Chen H, Shen Y. How to prevent in-hospital COVID-19 infection and reassure women about the safety of pregnancy: Experience from an obstetric center in China. J Int Med Res. 2020;48(7):300060520939337.doi:10.1177/0300060520939337

14 Justman N, Shahak G, Gutzeit O, et al. Lockdown with a Price: The impact of the COVID-19 Pandemic on Prenatal Care and Perinatal Outcomes in a Tertiary Care Center. Isr Med Assoc J. 2020;22(9):533-537.

15 Kugelman N, Lavie O, Assaf W, et al. Changes in the obstetrical emergency department profile during the COVID-19 pandemic [published online ahead of print, 2020 Nov 16]. J Matern Fetal Neonatal Med. 2020;1-7. doi:10.1080/14767058.2020.1847072

16 Institute of Medicine and National Research Council. Weight Gain during Pregnancy:Reexamining the Guidelines. In: Washington, DC:The National Academies Press; 2009:240-255.

17 WHO recommendations on antenatal care for a positive pregnancy experience. Published 2016. Accessed [Available from: www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/.]

18 Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46:348-355.

19 Xu S, Shao F, Bao B, et al. Clinical Manifestation and Neonatal Outcomes of Pregnant Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. Open Forum Infect Dis. 2020;7(7):ofaa283. Published 2020 Jul 5. doi:10.1093/ofid/ofaa283

20 Chen Y, Bai J. Maternal and infant outcomes of full-term pregnancy combined with COVID-2019 in Wuhan, China: retrospective case series. Arch Gynecol Obstet. 2020;302(3):545-551. doi:10.1007/s00404-020-05573-8

21 Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. Int J Gynaecol Obstet. 2020;150(3):312-317. doi:10.1002/ijgo.13265

22 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. doi:10.1016/j.ejogrb.2020.04.022

23 Khanghah AG, Khalesi ZB, Hassanzadeh R Afagh. The importance of depression during pregnancy. JBRA Assist Reprod. 2020;24(4):405-410. Published 2020 Oct 6. doi:10.5935/1518-0557.20200010

24 Wu Y, Lu YC, Jacobs M, et al. Association of Prenatal Maternal Psychological Distress With Fetal Brain Growth, Metabolism, and Cortical Maturation. JAMA Netw Open. 2020;3(1):e1919940. Published 2020 Jan 3. doi:10.1001/jamanetworkopen.2019.19940

25 Nabi G, Siddique R, Xiaoyan W, et al. COVID-19 induced psychosocial stressors during gestation: possible maternal and neonatal consequences. Curr Med Res Opin. 2020;36(10):1633-1634. doi:10.1080/03007995.2020.1815003

26 Gilles M, Otto H, Wolf IAC, et al. Maternal hypothalamus-pituitary-adrenal (HPA) system activity and stress during pregnancy: Effects on gestational age and infant's anthropometric measures at birth. Psychoneuroendocrinology. 2018;94:152-161. doi:10.1016/j.psyneuen.2018.04.022 27.

27 Wang L, Nabi G, Zhang T, Wu Y, Li D. Potential Neurochemical and Neuroendocrine Effects of Social Distancing Amidst the COVID-19 Pandemic. Front Endocrinol (Lausanne). 2020;11:582288. Published 2020 Oct 8. doi:10.3389/fendo.2020.582288

28 Coxon K, Turienzo CF, Kweekel L, et al. The impact of the coronavirus (COVID-19) pandemic on maternity care in Europe. Midwifery. 2020;88:102779. doi:10.1016/j.midw.2020.102779

29 National Health Commission of the People's Republic of China. Notice on strengthening maternal disease treatment and safe midwifery during the prevention and control of new coronavirus pneumonia. (accessed Feb 8, 2020) [Available from: http://www.nhc.gov.cn/xcs/zhengcwj/202002/4f80657b346e4d6ba76e2cfc3888c630.]

30 Zhao F, Xu Y, Chen YT, Cheng JY, Pan XY. Influence of the universal two-child policy on obstetric issues. Eur J Obstet Gynecol Reprod Biol. 2020;252:479-482. doi:10.1016/j.ejogrb.2020.07.028

31 Vivanti AJ, Deruelle P, Picone O, et al. Follow-up for pregnant women during the COVID-19 pandemic: French national authority for health recommendations. J Gynecol Obstet Hum Reprod. 2020;49(7):101804. doi:10.1016/j.jogoh.2020.101804

Table 1 Characteristics of 7699 pregnant women before and during the COVID-19 pandemic

Items	N / Mean (SD)	Pre COVID-19 (N,%; mean, SD)	COVID-19 (N,%; mean, SD)	χ^2/t	*P*
Maternal age (years)	30.07 (3.98)	29.92 (3.91)	30.29 (4.08)	-3.42	0.001
Maternal age (years)				8.262	0.016
≤24	487	297 (6.58)	190 (5.96)		
25-35	6117	3614 (80.12)	2503 (78.51)		
≥35	1095	600 (13.30)	495 (15.53)		
Ethnicity					
Han	7227	4236 (93.90)	2991 (93.82)	0.022	0.881
Other	472	275 (6.10)	197 (6.18)		
Occupation				0.202	0.653
Unemployed	911	528 (11.73)	383 (12.07)		
Employed	6762	3972 (88.27)	2790 (87.93)		
Education				7.782	0.051
Primary school or less	34	22 (0.49)	12 (0.38)		
Junior high school	578	355 (7.88)	223 (7.02)		
Senior high school	3774	2251 (49.94)	1523 (47.92)		
Undergraduate or above	3299	1879 (41.69)	1420 (44.68)		
Gravidity	1.99 (1.08)	1.99 (1.07)	2.00 (1.08)	-0.223	0.823

Gravidity				1.883	0.39
1	3068	1809 (40.10)	1259 (39.49)		
2	2523	1451 (32.17)	1072 (33.63)		
≥3	2108	1251 (27.73)	857 (26.88)		
Parity	0.43 (0.53)	0.43 (0.52)	0.44 (0.54)	-0.815	0.415
Parity				1.362	0.506
1	3195	1849 (40.99)	1346 (42.22)		
2	119	68 (1.51)	51 (1.60)		
≥3	4385	2594 (57.50)	1791 (56.18)		
History of miscarriage	0.09 (0.32)	0.08 (0.32)	0.09 (0.33)	-1.18	0.239
History of miscarriage	579	328 (7.27)	251 (7.87)	0.974	0.324
History of induced abortion	0.47 (0.76)	0.48 (0.76)	0.46 (0.76)	0.88	0.379
History of induced abortion	2601	1559 (34.58)	1042 (32.69)	2.982	0.084
Family history of chronic disease	929	481 (10.74)	448 (14.18)	20.536	<0.000 1
Pre-pregnancy BMI, kg/m^2	22.04 (3.12)	22.09 (3.17)	21.97 (3.17)	1.45	0.147
Pre-pregnancy BMI, kg/m^2				2.465	0.482
Underweight (18.5)	676	392 (8.69)	284 (8.91)		
Normal (18.5–24.9)	5717	3375 (74.82)	2342 (73.46)		
Overweight (25-29.9)	1079	610 (13.52)	469 (14.71)		
Obese (30)	227	134 (2.97)	93 (2.92)		
The rate of gestational weight	0.42 (0.09)	0.42 (0.09)	0.42 (0.09)	-1.035	0.301

gain (kg /week)					
Gestational weight gain				6.412	0.041
Insufficient	2115	1204 (26.69)	911 (28.58)		
Appropriate	3144	1894 (41.99)	1250 (39.21)		
Excessive	2440	1413 (31.32)	1027 (32.21)		
Prenatal visits	11.95 (3.25)	11.98 (3.27)	11.90 (3.23)	0.892	0.373
Prenatal visits				8.175	0.004
<8	824	521 (11.55)	303 (9.50)		
≥8	6875	3990 (88.45)	2885 (90.50)		
Total	7699	4511 (58.59)	3188 (41.41)		

Missing data: occupation, 26 (0.34%); education, 14 (0.18%); history of induced abortion, 2 (0.03%); and family history of chronic disease, 59 (0.77%).

Table 2 Pregnancy outcomes before and during the COVID-19 pandemic

Prevalence of outcomes (%)	Pre-COVID-19 (%)	COVID-19 (%)	χ^2	*P*
Adverse maternal outcomes				
Gestational diabetes[b]	1262 (27.99)	872 (27.38)	0.347	0.556
Gestational hypertension[b]	281 (6.23)	196 (6.15)	0.020	0.889
Premature rupture of membranes[b]	1385 (30.72)	1070 (33.59)	7.119	0.008
Caesarean section[b]	2065 (45.80)	1534 (48.16)	4.197	0.040
Adverse foetal outcomes				
Stillbirth	2 (0.04)	3 (0.09)	0.713	0.411[a]
Foetal distress[b]	527 (11.69)	418 (13.12)	3.574	0.059
Preterm birth[b]	199 (4.41)	121 (3.80)	1.767	0.184
Low birth weight[b]	137 (3.04)	96 (3.01)	0.004	0.951
Macrosomia[b]	304 (6.74)	213 (6.69)	0.009	0.925

Note: [a]Fisher exact test; [b]these pregnancy outcomes were all based on the data from 7694 live births.

Table 3 The influence of the COVID-19 pandemic on pregnancy outcomes

Pregnancy outcomes	Model A		Model B		Model C	
	cRR (95% CI)	P	aRR (95% CI)	P	aRR (95% CI)	P
Adverse maternal outcomes						
Gestational diabetes[b]	0.98 (0.91, 1.05)	0.556	0.97 (0.90, 1.05)	0.460	0.95 (0.88, 1.02)	0.136
Gestational hypertension[b]	0.99 (0.83, 1.18)	0.889	0.99 (0.83, 1.18)	0.920	0.96 (0.80, 1.14)	0.627
Premature rupture of membranes[b]	1.09 (1.02, 1.17)	0.007	1.10 (1.03, 1.17)	0.006	1.11 (1.04, 1.18)	0.003
Caesarean section[b]	1.05 (1.00, 1.10)	0.040	1.05 (1.00, 1.10)	0.055	1.05 (1.00, 1.10)	0.057
Adverse foetal outcomes						
Stillbirth	1.00 (1.00, 100)	0.427	1.00 (1.00, 1.00)	0.382	1.00 (1.00, 1.00)	0.387
Foetal distress[b]	1.12 (1.00, 1.27)	0.059	1.12 (1.00, 1.27)	0.061	1.14 (1.01, 1.29)	0.028
Preterm birth[b]	0.86 (0.69, 1.07)	0.184	0.84 (0.68, 1.05)	0.135	0.86 (0.69, 1.08)	0.190
Low birth weight[b]	0.99 (0.77, 1.28)	0.951	0.99 (0.77, 1.28)	0.954	1.00 (0.78, 1.30)	0.983
Macrosomia[b]	0.99 (0.84,	0.925	1.00 (0.85, 1.19)	0.999	1.00(0.85,	0.975

	1.17)	1.19)

Note: cRR, crude risk ratio; aRR, adjusted risk ratio; [b]these pregnancy outcomes were all based on the data from 7694 live births.

Model A: a univariate model without controlling for any confounding factors;

Model B: controls for demographic characteristics (age, ethnicity, occupation, and education);

Model C: based on Model B, supplemented to control for gravidity, parity, history of miscarriage, history of induced abortion, pregnancy BMI, gestational weight gain, family history of chronic disease, and the number of prenatal visits.

Figure 1 Interrupted time-series analysis of the impact of COVID-19 on premature rupture of membranes

Figure 2 Interrupted time-series analysis of the impact of COVID-19 on foetal distress

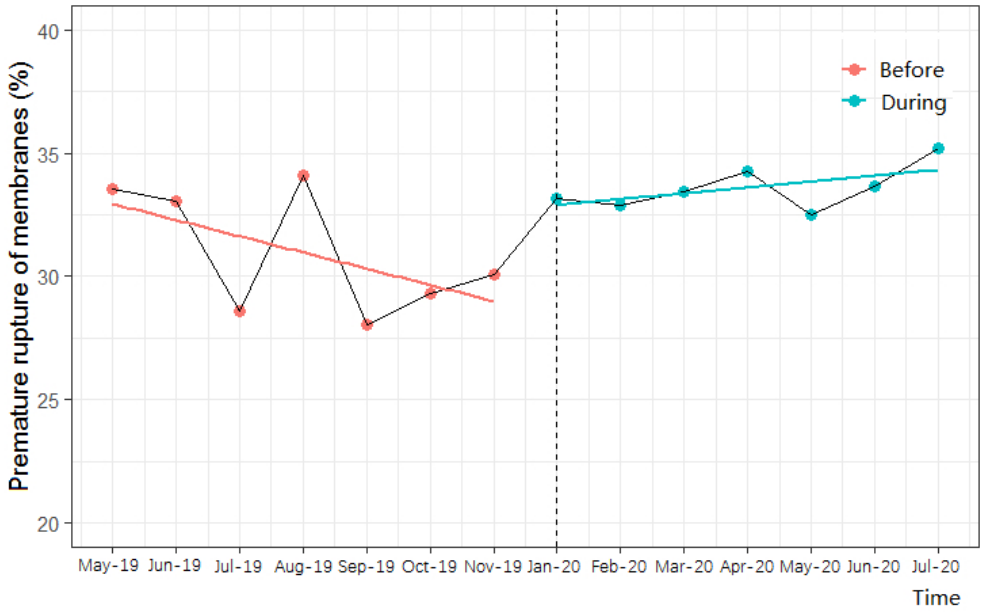


Figure 1 Interrupted time-series analysis of the impact of COVID-19 on premature rupture of membranes

194x123mm (96 x 96 DPI)

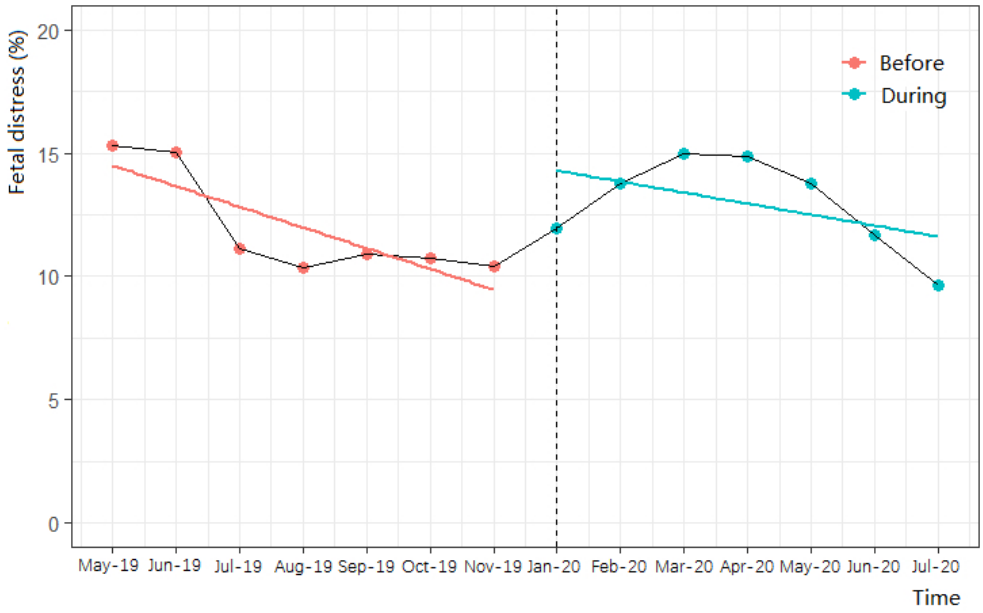


Figure 2 Interrupted time-series analysis of the impact of COVID-19 on foetal distress

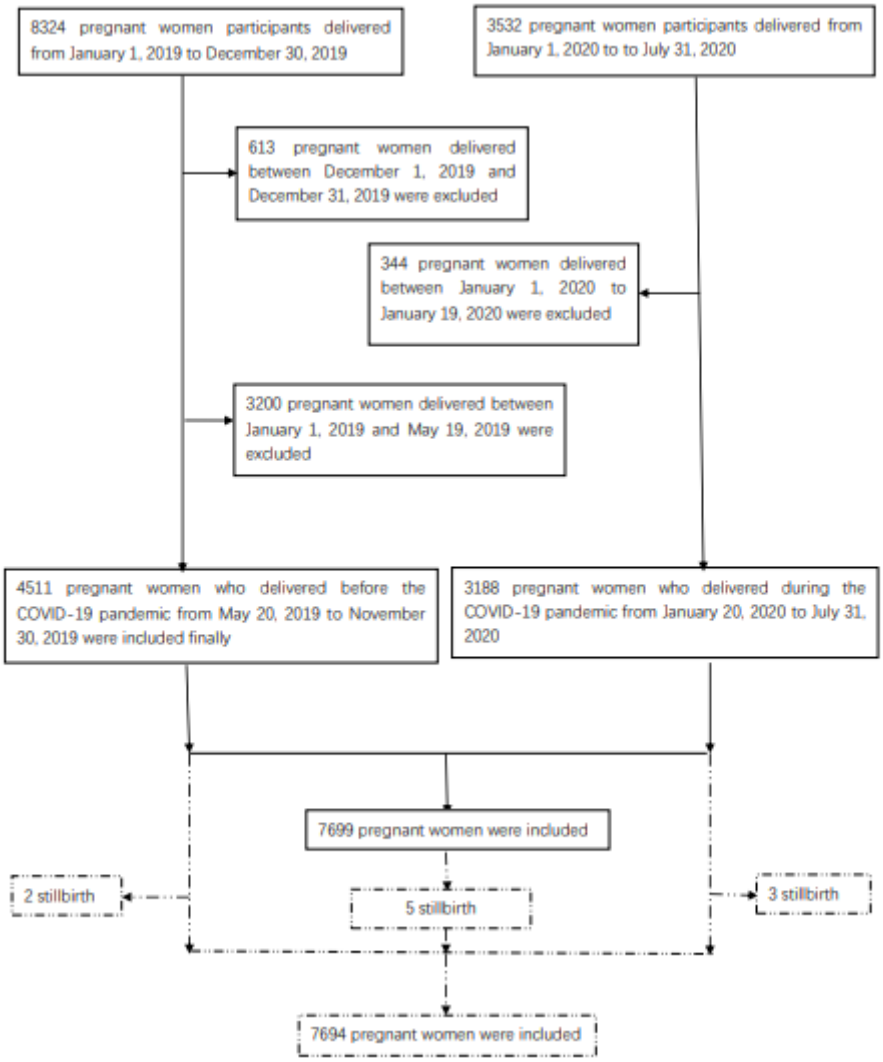
194x123mm (96 x 96 DPI)

Supplemental Table 1 Characteristics of 7694 pregnant women before and during COVID-19 pandemic

Items	N / Mean (SD)	Pre COVID-19 (N,%; mean, SD)	COVID-19 (N,%; mean, SD)	χ^2/t	*P*
Maternal age (years)	30.20 (3.95)	30.01 (3.89)	30.45 (4.03)	-4.771	<0.0001
Maternal age (years)				8.301	0.016
⩽24	487 (6.33)	297 (6.59)	190 (5.97)		
25-35	6112 (79.44)	3612 (80.11)	2500 (78.49)		
⩾35	1095 (14.23)	600 (13.31)	495 (15.54)		
Ethnicity				0.024	0.876
Han	7222 (93.87)	4234 (93.90)	2988 (93.81)		
Other	472 (6.13)	275 (6.10)	197 (6.19)		
Occupation				0.13	0.677
Unemployed	910 (11.87)	528 (11.74)	382 (12.05)		
Employed	6758 (88.13)	3970 (88.26)	2788 (87.95)		
Education				7.683	0.053
Primary school or less	33 (0.43)	21 (0.47)	12 (0.38)		
Junior high school	578 (7.53)	355 (7.88)	223 (7.02)		
Senior high school	3772 (49.11)	2251 (49.97)	1521 (47.91)		
Undergraduate or above	3297 (42.93)	1878 (41.69)	1419 (44,69)		
Gravidity	2.01 (1.10)	2.01 (1.13)	2.01 (1.07)	0.165	0.869
Gravidity				1.988	0.370
1	3067 (39.86)	1809 (40.12)	1258 (39.50)		
2	2522 (32.78)	1450 (32.16)	1072 (33.66)		
⩾3	2105 (27.36)	1250 (27.72)	855 (26.84)		
Parity	0.45 (0.53)	0.44 (0.53)	0.46 (0.54)	-1.178	0.239
Parity				1.370	0.504
1	3191 (41.47)	1847 (40.96)	1344 (42.20)		
2	119 (1.55)	68 (1.51)	51 (1.60)		
⩾3	4384 (56.98)	2594 (57.53)	1790 (56.20)		
History of miscarriage	0.08 (0.32)	0.08 (0.31)	0.09 (0.32)	-0.955	0.339
History of miscarriage	579 (7.72)	328 (7.27)	251 (7.88)	0.986	0.321
History of induced abortion	0.47 (0.77)	0.48 (0.78)	0.45 (0.76)	1.334	0.182
History of induced abortion	2598 (33.78)	1558 (34.57)	1040 (32.65)	3.061	0.080
Family history of chronic disease	927 (12.14)	480 (10.72)	447 (14.16)	20.540	<0.001
Pre-pregnancy BMI, kg/m^2	22.24 (3.33)	22.22 (3.30)	22.27 (3.36)	-0.564	0.573
Pre-pregnancy BMI, kg/m^2				2.467	0.481
Underweight (18.5)	676 (8.79)	392 (8.69)	284 (8.92)		
Normal (18.5–24.9)	5714 (74.27)	3374 (74.83)	2340 (73.47)		
Overweight (25-29.9)	1077 (14.00)	609 (13.51)	468 (14.69)		
Obese (30)	227 (2.95)	134 (2.97)	93 (2.92)		
The rate of gestational weight	0.42 (0.09)	0.42 (0.09)	0.42 (0.09)	-1.044	0.297

gain (kg /week)					
Gestational weight gain				6.338	0.042
Insufficient	2112 (27.45)	1203 (26.68)	909 (28.54)		
Appropriate	3142 (40.84)	1893 (41.98)	1249 (39.22)		
Excessive	2440 (31.71)	1413 (31.34)	1027 (32.24)		
Prenatal visits	11.89 (3.37)	11.91 (3.43)	11.86 (3.27)	0.562	0.574
Prenatal visits				8.225	0.004
<8	822 (10.68)	520 (11.53)	302 (9.48)		
⩾8	6872 (89.32)	3989 (88.47)	2883 (90.52)		
Total	7694 (100)	4509 (58.60)	3185 (41.40)		

Missing data: occupation 26 (0.34%), education 14 (0.18%) history of induced abortion 2 (0.03%), and family history of chronic disease 59 (0.77%).



Supplemental Figure 1 The diagram of included and excluded participants

Supplemental table 2 The influence of COVID-19 pandemic on pregnancy outcome

Pregnancy outcomes	Model C (full model)	
	aRR (95%CI)	P
Maternal adverse outcomes		
Gestational diabetes[b]	0.93 (0.87, 1.01)	0.066
Gestational hypertension[b]	0.94 (0.77, 1.14)	0.52
Premature rupture of membranes[b]	1.10 (1.03, 1.20)	0.007
Caesarean section[b]	1.04 (0.98, 1.10)	0.189
Fetal adverse outcomes		
Stillbirth	1.00 (1.00, 1.00)	0.647
Fetal distress[b]	1.14 (1.01, 1.28)	0.033
Preterm birth[b]	0.75 (0.56, 1.02)	0.063
Low birth weight[b]	0.87 (0.61, 1.24)	0.441
Macrosomia[b]	1.05 (0.87, 1.26)	0.608

Note：aRR, adjusted risk ratio; b these pregnancy outcomes all based on 7694 live birth data. Model C: controlling maternal age, ethnicity, occupation, education, gravidity, parity, history of miscarriage, history of induced abortion, pregnancy BMI, the rate of gestational weight gain, family history of chronic disease, the number of prenatal visit.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	17
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	4-5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047900.R1
Article Type:	Original research
Date Submitted by the Author:	09-Feb-2021
Complete List of Authors:	Du, Min; Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China Yang, Jie; Maternal and Child Health Hospital of Tongzhou District, Beijing, China. Han, Na; Maternal and Child Health Hospital of Tongzhou District, Beijing, China. Liu, Min ; Peking University, School of Public Health, Department of Epidemiology & Biostatistics Liu, Jue; Peking University School of Public Health, Department of Epidemiology & Biostatistics
Primary Subject Heading:	Public health
Secondary Subject Heading:	Public health, Epidemiology, Infectious diseases, Obstetrics and gynaecology
Keywords:	COVID-19, Public health < INFECTIOUS DISEASES, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title: Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

Authors: Min Du[1*], Jie Yang[2*], Na Han[2], Min Liu[1], Jue Liu[1,3]

[*]Contributed equally.

Running title: COVID-19 pandemic and pregnancy outcome

Affiliations:

[1] Department of Epidemiology and Biostatistimcs, School of Public Health, Peking University, Beijing, China

[2] Maternal and Child Health Hospital of Tongzhou District, Beijing, China

[3] National Health Commission Key Laboratory of Reproductive Health, Peking University Health Science Center

Address correspondence to: Dr. Jue Liu, Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China.

E-mail address: jueliu@bjmu.edu.cn

Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

ABSTRACT

Objectives The secondary impacts of the COVID-19 pandemic on adverse maternal and neonatal outcomes remain unclear. In this study, we aimed to evaluate the association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes.

Design We conduced retrospective analyses on 2 cohorts comprising 7699 pregnant women in Beijing, China, and compared pregnancy outcomes between the pre-COVID-2019 cohort (women who delivered from May 20, 2019 to November 30, 2019) and the COVID-2019 cohort (women who delivered from January 20, 2020 to July 31, 2020). The secondary impacts of the COVID-2019 pandemic on pregnancy outcomes were assessed by using multivariate log-binomial regression models, and we used interrupted time-series regression (ITS) analysis to further control the effects of time-trends.

Setting One tertiary-level centre in Beijing, China

Participants 7699 pregnant women.

Results Compared with women in the pre-COVID-19 pandemic group, pregnant women during the COVID-2019 pandemic were more likely to be of advanced age, exhibit insufficient or excessive gestational weight gain, and show a family history of chronic disease (all $P<0.05$). After controlling for other confounding factors, the risk of premature rupture of membranes and foetal distress was increased by 11% (95% CI, 1.04, 1.18; $p < 0.01$) and 14% (95% CI, 1.01, 1.29; $p < 0.05$), respectively, during the COVID-2019 pandemic. The association still remained in the ITS analysis after additionally controlling for time-trends (all $P<0.01$). We uncovered no other associations between the COVID-19 pandemic and other pregnancy outcomes ($P >0.05$).

Conclusions During the COVID-19 pandemic, more women manifested either insufficient or excessive gestational weight gain; and the risk of premature rupture of membranes and foetal distress was also higher during the pandemic.

Keywords: COVID-19, pregnancy outcome, cohort study

Strengths and limitations of this study

A major strength of this study was our estimation of the secondary impacts of the COVID-19 pandemic on adverse maternal and neonatal outcomes in China, the first such study of its kind.

We collected materials from the hospital-information system, which assured the accuracy of our data.

This study was of a retrospective nature and thus did not include physical exercise, diet, or psychological status, which might also be related to pregnancy outcomes.

The follow-up period in this study was only until delivery, such that the long-term impacts of the COVID-19 pandemic on women and their infants could not be explored.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has developed into the largest and deadliest pandemic respiratory disease. As of August 23, 2020, a total of 23,057,288 cases and 800,906 deaths have been reported to the World Health Organization (WHO). Perinatal research on COVID-19 is now primarily focused on pregnancy outcomes of women infected with SARS-CoV-2—including caesarean section[1,2], foetal distress[1], preterm birth[3], and even maternal death[4]. However, the adverse secondary impacts of the COVID-19 pandemic on maternal and neonatal outcomes remain unknown.

Several investigators have explored the effects of the COVID-19 pandemic on the mental health of pregnant women[5-8]. Ahorsu et al. found that the fear of COVID-19 was associated with depression, suicidal intention, adverse mental-health effects, and diminished overall quality of life among pregnant women[5]. Some studies showed that the COVID-19 pandemic was associated with obstetric care[9-12]—including institutional deliveries, high-risk pregnancy[9], intrapartum foetal heart rate monitoring, breastfeeding within 1 h of birth[10], and prenatal diagnosis/screening tests; while others have shown an effect of the pandemic on causing adverse maternal and neonatal outcomes[9,10,13-15]. The COVID-19 pandemic was associated with higher percentages of gestational hypertension[13,14], gestational diabetes[14], and premature rupture of membranes[15]. Goyal et al. reported that there was an increased rate of admission to the intensive care unit for pregnant women during the pandemic, compared with prior to COVID-19[9]. Ashish et al. also found that both

the rate of institutional stillbirth and institutional neonatal mortality increased significantly during the lockdown period in Nepal[10].

However, a majority of investigators [9,10,13-15] have only compared the rate of adverse maternal and neonatal outcomes between the pre-COVID-19 period and the COVID-19 pandemic period without controlling important factors related to adverse pregnancy outcomes (e.g., parity, gestational weight gain, or a family history of chronic disease). Thus, it is evident that more research is needed regarding the effects of the pandemic on some specific adverse outcomes, including caesarean section, foetal distress, low birth weight, and macrosomia. Unfortunately, in none of the previously aforementioned studies was there an examination of the association between the COVID-19 pandemic and adverse pregnancy outcomes in mainland China.

Therefore, we aimed in the present study to evaluate the secondary impacts of the COVID-19 pandemic on the risk of adverse pregnancy outcomes, using two cohorts (a pre-COVID-19 cohort and a COVID-19 cohort) to provide evidence for the implementation of targeted strategies that promote maternal and infant health during the COVID-19 pandemic.

METHODS

Study population

Two retrospective cohorts (pre-COVID-19 and during COVID-19) were analysed in this study, using the following inclusion criteria: (1) women with singleton pregnancies, (2) pregnant women who made prenatal visits to the Maternal and Child Health Hospital of Tongzhou District in Beijing, and (3) women who delivered between 2019 and July 31, 2020.

There were 8324 pregnant women who gave birth between January 1, 2019 and December 31, 2019; and 3532 pregnant women who gave birth between January 1, 2020 and July 31, 2020. Although we herein focused on the overall effects of the COVID-19 pandemic, none of the participants was infected with SARS-CoV-2 (the virus that causes *COVID-19*), given that the first case in China was reported in December 2019 and the first case in Beijing was reported in January 2020. To better assess the influence of the COVID-19 pandemic locally, we excluded the 613 participants who delivered during December 2019; the 344 women who delivered between January 1, 2020 and January 19, 2020; and also the 3202 pregnant women who delivered between January 1, 2019 and May 19, 2019. Because we decided to only make close temporal comparisons

in order to avoid certain potentially confounding factors (e.g., differing policies between 2019 and 2020), we chose women who delivered from May 20, 2019 to November 30, 2019 as the pre-COVID-19 cohort; and those who delivered from January 20, 2020 to July 31, 2020 as the COVID-19 cohort. We thus included 4511 pregnant women in the pre-COVID-19 cohort and 3188 pregnant women in the COVID-19 cohort. However, in order to estimate the effects of the COVID-19 pandemic on other pregnancy outcomes (e.g., preterm birth and low birth weight), we excluded two stillbirth in the pre-COVID-19 cohort and three stillbirths in the COVID-19 cohort. We therefore ultimately included 4509 pregnant women who gave birth prior to the COVID-19 pandemic and 3185 pregnant women who gave birth during the COVID-19 pandemic (supplemental Figure 1 and supplemental Table 1). This study was approved by the Institutional Review Boards at Peking University (IRB00001052-18003).

Data collection

Data were collected from the hospital-information system, including basic demographic characteristics (age, ethnicity, occupation, and education), pregnancy status (gravidity, parity, history of miscarriage, and history of induced abortion), health status (pre-pregnancy body mass index [BMI]), gestational weight gain, a family history of chronic disease, and the number of prenatal visits. Of these characteristics, pre-pregnancy BMI was categorized based on the WHO cut-off points; gestational weight gain was calculated as the difference between weight at the last routine pregnancy visit and the pre-pregnancy weight; and the rate of gestational weight gain was calculated as the gestational weight gain/the gestational weeks at the last routine pregnancy visit. Categorization was in accordance with IOM criteria: gestational weight gain was classified as insufficient, appropriate, or excessive[16]; and a family history of chronic disease was principally with respect to whether the maternal parents or maternal grandparents manifested cardiovascular diseases such as heart disease and diabetes. The number of prenatal visits was not fewer than 8 times per year as recommended by the WHO[17].

Assessment of pregnancy outcomes

For this study we obtained information on pregnancy outcomes according to the ICD codes of discharge diagnosis, including gestational hypertension, gestational diabetes (GDM), premature rupture of membranes, delivery mode, stillbirth, foetal distress, preterm birth, low birth weight, and macrosomia. Preterm birth was defined as less than 37 weeks of gestation based on the

interval between the last menstrual period and the date of delivery of the baby. Delivery mode was categorized as either caesarean section or vaginal delivery. Caesarean section included both medical and psychosocial indications, and vaginal delivery included spontaneous vaginal and assisted vaginal births. Infant birth weight was divided into low birth weight (< 2500 g) and macrosomia (> 4000 g).

Statistical analyses

We compared the characteristics of women before and during the COVID-19 pandemic by using the χ^2 or *t* test. The χ^2 test was also used to compare pregnancy outcomes of women before and during the pandemic. Given that odds ratios (ORs) cannot provide accurate estimates for the relative risks (RRs) in the cohort studies, we used univariate and multivariate log-binomial regression models to estimate the crude risk ratios (cRRs) and adjusted risk ratios (aRRs) of the impacts of the COVID-19 pandemic on adverse pregnancy outcomes using the SAS Software Package V.9.4, (SAS Institute). We also calculated the attributable risk percentage (AR%, 95% CI). We performed sensitivity analysis by fitting different models to examine the robustness of the estimation, and 3 models were fitted. The first (model A) was unadjusted; the second (model B) was adjusted for baseline demographic characteristics (maternal age, ethnicity, occupation, education); and the third model (full-model C) was further adjusted for pregnancy condition (gravidity, parity, history of miscarriage, history of induced abortion) and health status (pre-pregnancy BMI, gestational weight gain [GWG], family history of chronic disease, and the number of prenatal visits). We additionally added a full-model C by replacing categorical variables with continuous variables, including maternal age, gravidity, parity, history of miscarriage, history of induced abortion, pre-pregnancy BMI, the rate of gestational weight gain, and the number of prenatal visits. Since interrupted time-series regression (ITS) analysis is useful for evaluating population-level health interventions with a clearly defined point in time [18], we conducted ITS to examine the impacts of COVID-19 on pregnancy outcomes using R 3.4.2 (R-team)[18]. A 2-sided value of $P<0.05$ was considered to be statistically significant for all of the analyses.

Patient and Public Involvement

No patients were involved in this anonymous data set.

RESULTS

A total of 7699 women were included in this study, with a mean age of 30.07 (±3.98, SD) and an average gestational week of 38.90 (± 1.46) weeks; 93.87% were of Han ethnicity, 11.83% were unemployed, and 56.97% had a bachelor's degree or less. Characteristics of the study population are provided in **Table 1**. Compared with women in the pre-COVID-19 pandemic group, pregnant women during the COVID-19 pandemic were more likely to be of advanced age (15.53% vs. 13.30%, respectively), show insufficient (28.58% vs. 26.69%) or excessive gestational weight gain (32.21% vs. 31.32%), have a family history of chronic disease (14.18% vs 10.74%), and have ⩾8 prenatal visits (9.50% vs. 11.55%, respectively; all *P*<0.05). Other characteristics were not significantly different between the two groups (all *P*>0.05).

The prevalences of caesarean sections and premature rupture of membranes were higher during the COVID-19 pandemic period compared with women prior to the pandemic (48.16% vs. 45.80%, *P*=0.040; and 33.59% vs. 30.72%, respectively; *P*=0.008). However, the prevalences of other pregnancy outcomes were not significantly different during the COVID-19 pandemic compared with the pre-pandemic period (*P*>0.05, **Table 2**).

In our log-binomial regression models, and after adjusting for all confounding factors, the risk for premature rupture of membranes and foetal distress during the COVID-19 pandemic compared to pre-COVID-19 women was increased by 11% (95% CI, 1.04, 1.18; p < 0.01) and 14% (95% CI, 1.01, 1.29; p < 0.05), respectively (**Table 3**). Additionally, the attributable risk percentage of the COVID-19 pandemic on premature rupture of membranes was 9.91 (95% CI, 3.84, 15.25), and the attributable risk percentage of the pandemic on foetal distress was 12.28 (95% CI, 0.99, 22.48). However, we uncovered no other associations between the COVID-19 pandemic and other pregnancy outcomes, and demonstrated similar results for the additional full-model C (as shown in supplemental Table 2). After controlling for time-trends in the interrupted time-series regression, the COVID-19 pandemic was still associated with an increased risk of premature rupture of membranes (*P*<0.001, Figure **1**) and foetal distress (*P*<0.01, Figure **2**).

DISCUSSION

Summary of the findings

To the best of our knowledge, this is the first cohort study to focus on secondary impacts of the COVID-19 pandemic on pregnancy outcomes in mainland China. Herein, we showed that more

pregnant women were of advanced age, with abnormal gestational weight gain, and a family history of chronic disease during the COVID-19 pandemic. The risks of premature rupture of membranes and foetal distress among pregnant women who gave birth during the COVID-19 pandemic were also higher than in those women who gave birth before the pandemic.

Strengths and limitations

The strengths of this study included its cohort-study design and use of well-established methods to detect the impacts of the COVID-19 pandemic on pregnancy outcomes, and we thus included two cohorts (a pre-COVID-19 cohort and a COVID-19 cohort), using the same study site. In addition, using log-binomial regression models and interrupted time-series analysis, we were able to evaluate the impact of a policy change or natural intervention (such as a pandemic).

There were some limitations to our study. First, this study was a retrospective study. We did not collect data on physical exercise, diet, or psychological status, which might also be related to pregnancy outcomes. The follow-up period for this study was only up to delivery, such that long-term impacts of the COVID-19 pandemic on women and their infants could not be explored. Second, this is a single-centre cohort study, and we only included participants at 1 hospital in Beijing. Therefore, these results may have limited relevance to other health-care systems outside of Beijing. Larger and multi-centre prospective cohort studies are therefore needed in the future to confirm and clarify the findings of our study. Finally, due to the lack of specific individual obstetric-management records, we could not investigate the impacts of specific measures on pregnancy outcomes.

Comparison with other studies

Although researchers had previously found that the prevalence of premature rupture of membranes in pregnant women infected with the novel coronavirus was relatively high[2,19-21], few had explored the secondary impacts of the COVID-19 pandemic on this adverse pregnancy outcome. Kugelman et al. found that there was a higher proportion of women who had premature rupture of membranes in a COVID-19 cohort (20.6% vs. 11.0%, p<0.001)[15]; and in the present study, we also found that the proportion of women who presented with premature rupture of membranes was higher in the COVID-19 cohort (33.59% vs. 30.72%, *P*=0.008). Compared to women pre-COVID-19, we observed that the risk of premature rupture of membranes during the COVID-19 pandemic was increased by 11% (95% CI, 1.04, 1.18; p < 0.01).

Premature rupture of membranes may additionally be associated with increased maternal anxiety during the COVID-19 pandemic[6,7]. Studies have shown that as the severity of the pandemic increased, the level of anxiety among pregnant women also increased [22]; and that maternal anxiety and depression were associated with premature rupture of membranes[23] because of the decreased levels of creatinine and choline[24] and an altered diurnal pattern of cortisol (manifested as a flattened cortisol decline and higher evening cortisol) [25,26]. We also found that the risk of foetal distress was increased during the pandemic, but noted a general lack of published research on this topic. The association might be related to enhanced psychological, neuroendocrine, and neurochemical changes caused by social-isolation stress during the COVID-19 pandemic[27]. Many countries took measures to control the transmission of the virus by keeping social distance (e.g., stay-at-home orders, the cancellation of public events, lockdown), which may increase the risk of social-isolation stress for pregnant women[27]. In one study, it was reported that one-third of women underwent an inadequate number of antenatal visits because of the lockdown for fear of contracting infection, resulting in 44.7% of pregnancies showing complications[9]. In addition, women pregnant during the COVID-19 pandemic might not have visited the hospital as frequently as in a non-pandemic time, which might have led to under instruction in perinatal healthcare and inadequate receipt of routine medical services[28]. However, the specific mechanism(s) underlying the effects on pregnancy of the COVID-19 pandemic remains unclear. In order to reduce the impact of COVID-19 pandemic on psychological health and increase the usage of perinatal healthcare for pregnant women during the pandemic, the National Health Commission of China launched a new notice on February 8, 2020 that proposed strengthening health counselling, screening, and follow-ups for pregnant women[29]. Besides, local hospital had tried their best to ensure the access to prenatal care by taking comprehensive measures (e.g., online appointment service, online consultation work, outpatient service and so on) to minimize the influence of COVID-19 pandemic on pregnancy and medical services. Nevertheless, our study showed that the secondary impacts of COVID-19 on pregnant women should draw greater attention, especially with respect to the premature rupture of membranes and foetal distress.

In our study, the prevalence of caesarean sections among pregnant women experiencing the COVID-19-pandemic was higher than in the group prior to the pandemic, which may be related to the higher proportions of caesarean-section indices that included foetal distress. We also found

that there was a greater proportion of women aged ≥35 years in the COVID-19 cohort, and that this cohort contained more women with a family history of chronic disease. This might be related to the implementation of the two-child policy since 2016 in China that more women with advanced maternal age were willing to have babies[30]. Zhao et al. found that the percentages of older pregnant women increased significantly in 2017 and 2018 compared with numbers in 2014, 2015 and 2016[31]. A steadily increased proportion of pregnant women with advanced age has been observed in recent years [32]. Correspondingly, family members of old pregnant women were more likely to have a history of chronic diseases. What's more, the impact of second-child policy might be greater in 2020 than that in 2019 due to the policies of isolation in home and travel restrictions. Kugelman et al. also found that women visited the obstetrical emergency department at a more advanced mean gestational age during the pandemic outbreak, compared with the pre-COVID period[15]. Pregnant women who visit outpatient clinics should also be followed as often as possible, and the psychological and emotional states of these women should be assessed and monitored in follow-up visits to address the possible risks of adverse pregnancy complications and outcomes[33].

Implications for clinicians and policymakers

Pregnant women should be considered as key populations in strategies focusing on management during COVID-19 pandemic. Service provision during the epidemic is needed to ensure the early identification and intervention of high-risk pregnant women. To ensure the access to prenatal care, hospital should take comprehensive and case-by-case measures, assess and monitor in follow-up visits as often as possible[33]. Additionally, except for healthcare services, pregnant women should be educated about the importance of regular visits, healthy lifestyle and reasonable precautions but not at the cost of compromising health (wearing masks, personal hygiene, etc.). The indirect impact of COVID-19 pandemic on the vulnerable pregnant women is needed to paid more attention to. Additionally, long-term impact and the mechanism of COVID-19 pandemic on pregnant women and their babies should be explored in the future to ensure the maternal and new-borns health by lager multi-centre cohort study.

CONCLUSIONS

In summary, we found that there were more pregnant women with abnormal gestational weight gain during the COVID-19 pandemic. The risk for premature rupture of membranes and foetal distress in pregnant women during the pandemic was also higher than in pregnant women before

the COVID-19 pandemic. Our findings highlight the importance of improved management during pregnancy to reduce adverse maternal and infant outcomes, especially with respect to premature rupture of membranes and foetal distress. Cohort studies are needed to assess the long-term direct and indirect impact of COVID-19 pandemic on maternal and child health in the future.

Contributors All the authors have made substantial contributions to the conception, design of the work; or the acquisition, analysis, or interpretation of data for the work. They have participated in drafting the manuscript and approval of the version to be published. Conceptualization: Jue Liu. Methodology: Jue Liu, Min Liu. Investigation: Min Du, Jie Yang, Jue Liu. Data acquisition: Jie Yang, Na Han. Data Curation: Min Du, Jie Yang, Jue Liu. Data analysis: Min Du, Jie Yang. Preparation of tables and figures: Min Du. Initial draft of manuscript: Min Du, Jie Yang, Jue Liu. Writing – Review & Editing: Na Han, Min Liu, Jue Liu. Supervision: Jue Liu.

Funding This research was funded by the National Natural Science Foundation of China (grant number 81703240), the National Science and Technology Key Projects on Prevention and Treatment of Major Infectious Diseases of China (2020ZX10001002), and the National Key Research and Development Project of China (grant number 2020YFC0846300).

Competing interests All authors report no conflict of interest.

Patient consent for publication Not required.

Ethics approval This study was approved by the Institutional Review Boards at Peking University (IRB00001052-18003).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request to the corresponding author.

REFERENCE

1 Gao YJ, Ye L, Zhang JS, et al. Clinical features and outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2020;20:564.

2 Zhang L, Dong L, Ming L, et al. Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection during late pregnancy: a report of 18 patients from Wuhan, China. BMC Pregnancy Childbirth. 2020;20:394.

3 Lokken EM, Walker CL, Delaney S, et al. Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington State [published online ahead of print, 2020 May 19]. Am J Obstet Gynecol. 2020;S0002-9378(20)30558-5.

4 Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. Am J Obstet Gynecol. 2020;223:109.e1-109.e16.

5 Ahorsu DK, Imani V, Lin CY, et al. Associations Between Fear of COVID-19, Mental Health, and Preventive Behaviours Across Pregnant Women and Husbands: An Actor-Partner Interdependence Modelling [published online ahead of print, 2020 Jun 11]. Int J Ment Health Addict. 2020;1-15. doi:10.1007/s11469-020-00340-x6.

6 Berthelot N, Lemieux R, Garon-Bissonnette J, et al. Uptrend in distress and psychiatric symptomatology in pregnant women during the coronavirus disease 2019 pandemic. Acta Obstet Gynecol Scand. 2020;99:848-855.

7 Hessami K, Romanelli C, Chiurazzi M, Cozzolino M. COVID-19 pandemic and maternal mental health: a systematic review and meta-analysis [published online ahead of print, 2020 Nov 1]. J Matern Fetal Neonatal Med. 2020;1-8. doi:10.1080/14767058.2020.1843155

8 Lemieux R, Garon-Bissonnette J, Loiselle M, Martel É, Drouin-Maziade C, Berthelot N. Association entre la fréquence de consultation des médias d'information et la détresse psychologique chez les femmes enceintes durant la pandémie de COVID-19: Association between news media consulting frequency and psychological distress in pregnant women during the COVID-19 pandemic [published online ahead of print, 2020 Oct 21]. Can J Psychiatry. 2020;706743720963917. doi:10.1177/0706743720963917

9 Goyal M, Singh P, Singh K, Shekhar S, Agrawal N, Misra S. The effect of the COVID-19 pandemic on maternal health due to delay in seeking health care: Experience from a tertiary center [published online ahead of print, 2020 Oct 31]. Int J Gynaecol Obstet. 2020;10.1002/ijgo.13457. doi:10.1002/ijgo.13457

10 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. doi:10.1016/S2214-109X(20)30345-4

11 Lalaguna Mallada P, Díaz-Gómez NM, Costa Romero M, San Feliciano Martín L, Gabarrell Guiu C. Impacto de la pandemia de Covid-19 en la lactancia y cuidados al nacimiento. Importancia de recuperar las buenas prácticas [The impact of Covid-19 pandemic on breastfeeding and birth care. The importance of recovering good practices.]. Rev Esp Salud Publica. 2020;94:e202007083. Published 2020 Jul 9.12.

12 Ozalp M, Demir O, Akbas H, Kaya E, Celik C, Osmanagaoglu MA. Effect of COVID-19 pandemic process on prenatal diagnostic procedures [published online ahead of print, 2020 Sep 1]. J Matern Fetal Neonatal Med. 2020;1-6. doi:10.1080/14767058.2020.1815190

13 Gu XX, Chen K, Yu H, Liang GY, Chen H, Shen Y. How to prevent in-hospital COVID-19 infection and reassure women about the safety of pregnancy: Experience from an obstetric center in China. J Int Med Res. 2020;48(7):300060520939337.doi:10.1177/0300060520939337
14 Justman N, Shahak G, Gutzeit O, et al. Lockdown with a Price: The impact of the COVID-19 Pandemic on Prenatal Care and Perinatal Outcomes in a Tertiary Care Center. Isr Med Assoc J. 2020;22(9):533-537.
15 Kugelman N, Lavie O, Assaf W, et al. Changes in the obstetrical emergency department profile during the COVID-19 pandemic [published online ahead of print, 2020 Nov 16]. J Matern Fetal Neonatal Med. 2020;1-7. doi:10.1080/14767058.2020.1847072
16 Institute of Medicine and National Research Council. Weight Gain during Pregnancy: Reexamining the Guidelines. In: Washington, DC:The National Academies Press; 2009:240-255.
17 WHO recommendations on antenatal care for a positive pregnancy experience. Published 2016. Accessed [Available from: www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/.]
18 Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46:348-355.
19 Xu S, Shao F, Bao B, et al. Clinical Manifestation and Neonatal Outcomes of Pregnant Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. Open Forum Infect Dis. 2020;7(7):ofaa283. Published 2020 Jul 5. doi:10.1093/ofid/ofaa283
20 Chen Y, Bai J. Maternal and infant outcomes of full-term pregnancy combined with COVID-2019 in Wuhan, China: retrospective case series. Arch Gynecol Obstet. 2020;302(3):545-551. doi:10.1007/s00404-020-05573-8
21 Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. Int J Gynaecol Obstet. 2020;150(3):312-317. doi:10.1002/ijgo.13265
22 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. doi:10.1016/j.ejogrb.2020.04.022
23 Khanghah AG, Khalesi ZB, Hassanzadeh R Afagh. The importance of depression during pregnancy. JBRA Assist Reprod. 2020;24(4):405-410. Published 2020 Oct 6. doi:10.5935/1518-0557.20200010
24 Wu Y, Lu YC, Jacobs M, et al. Association of Prenatal Maternal Psychological Distress With Fetal Brain Growth, Metabolism, and Cortical Maturation. JAMA Netw Open. 2020;3(1):e1919940. Published 2020 Jan 3. doi:10.1001/jamanetworkopen.2019.19940
25 Nabi G, Siddique R, Xiaoyan W, et al. COVID-19 induced psychosocial stressors during gestation: possible maternal and neonatal consequences. Curr Med Res Opin. 2020;36(10):1633-1634. doi:10.1080/03007995.2020.1815003
26 Gilles M, Otto H, Wolf IAC, et al. Maternal hypothalamus-pituitary-adrenal (HPA) system activity and stress during pregnancy: Effects on gestational age and infant's anthropometric measures at birth. Psychoneuroendocrinology. 2018;94:152-161. doi:10.1016/j.psyneuen.2018.04.022 27.

27 Wang L, Nabi G, Zhang T, Wu Y, Li D. Potential Neurochemical and Neuroendocrine Effects of Social Distancing Amidst the COVID-19 Pandemic. Front Endocrinol (Lausanne). 2020;11:582288. Published 2020 Oct 8. doi:10.3389/fendo.2020.582288

28 Coxon K, Turienzo CF, Kweekel L, et al. The impact of the coronavirus (COVID-19) pandemic on maternity care in Europe. Midwifery. 2020;88:102779. doi:10.1016/j.midw.2020.102779

29 National Health Commission of the People's Republic of China. Notice on strengthening maternal disease treatment and safe midwifery during the prevention and control of new coronavirus pneumonia. (accessed Feb 8, 2020) [Available from: http://www.nhc.gov.cn/xcs/zhengcwj/202002/4f80657b346e4d6ba76e2cfc3888c630.]

30 Liu J, Liu M, Zhang S, Ma Q, Wang Q. Intent to have a second child among Chinese women of childbearing age following China's new universal two-child policy a cross-sectional study. BMJ Sex Reprod Health 2019;46(1):59-66. doi:10.1136/bmjsrh-2018-200197.

31 Zhao F, Xu Y, Chen YT, Cheng JY, Pan XY. Influence of the universal two-child policy on obstetric issues. Eur J Obstet Gynecol Reprod Biol. 2020;252:479-482. doi:10.1016/j.ejogrb.2020.07.028

32 Liu J, Song L, Qiu J, Jing W, Wang L, Dai Y, Qin G, Liu M. Reducing maternal mortality in China in the era of the two-child policy. BMJ Glob Health. 2020;5(2):e002157. doi: 10.1136/bmjgh-2019-002157.

33 Vivanti AJ, Deruelle P, Picone O, et al. Follow-up for pregnant women during the COVID-19 pandemic: French national authority for health recommendations. J Gynecol Obstet Hum Reprod. 2020;49(7):101804. doi:10.1016/j.jogoh.2020.101804

Table 1 Characteristics of 7699 pregnant women before and during the COVID-19 pandemic

Items	N / Mean (SD)	Pre COVID-19 (N,%; mean, SD)	COVID-19 (N,%; mean, SD)	χ^2/t	*P*
Maternal age (years)	30.07 (3.98)	29.92 (3.91)	30.29 (4.08)	-3.42	0.001
Maternal age (years)				8.262	0.016
≤24	487	297 (6.58)	190 (5.96)		
25-35	6117	3614 (80.12)	2503 (78.51)		
≥35	1095	600 (13.30)	495 (15.53)		
Ethnicity					
Han	7227	4236 (93.90)	2991 (93.82)	0.022	0.881
Other	472	275 (6.10)	197 (6.18)		
Occupation				0.202	0.653
Unemployed	911	528 (11.73)	383 (12.07)		
Employed	6762	3972 (88.27)	2790 (87.93)		
Education				7.782	0.051
Primary school or less	34	22 (0.49)	12 (0.38)		
Junior high school	578	355 (7.88)	223 (7.02)		
Senior high school	3774	2251 (49.94)	1523 (47.92)		
Undergraduate or above	3299	1879 (41.69)	1420 (44.68)		
Gravidity	1.99 (1.08)	1.99 (1.07)	2.00 (1.08)	-0.223	0.823
Gravidity				1.883	0.39
1	3068	1809 (40.10)	1259 (39.49)		
2	2523	1451 (32.17)	1072 (33.63)		
≥3	2108	1251 (27.73)	857 (26.88)		
Parity	0.43 (0.53)	0.43 (0.52)	0.44 (0.54)	-0.815	0.415
Parity				1.362	0.506
1	3195	1849 (40.99)	1346 (42.22)		
2	119	68 (1.51)	51 (1.60)		
≥3	4385	2594 (57.50)	1791 (56.18)		
History of miscarriage	0.09 (0.32)	0.08 (0.32)	0.09 (0.33)	-1.18	0.239
History of miscarriage	579	328 (7.27)	251 (7.87)	0.974	0.324
History of induced abortion	0.47 (0.76)	0.48 (0.76)	0.46 (0.76)	0.88	0.379
History of induced abortion	2601	1559 (34.58)	1042 (32.69)	2.982	0.084
Family history of chronic disease	929	481 (10.74)	448 (14.18)	20.536	<0.0001
Pre-pregnancy BMI, kg/m^2	22.04 (3.12)	22.09 (3.17)	21.97 (3.17)	1.45	0.147
Pre-pregnancy BMI, kg/m^2				2.465	0.482
Underweight (18.5)	676	392 (8.69)	284 (8.91)		
Normal (18.5–24.9)	5717	3375 (74.82)	2342 (73.46)		
Overweight (25-29.9)	1079	610 (13.52)	469 (14.71)		
Obese (30)	227	134 (2.97)	93 (2.92)		
The rate of gestational weight gain (kg /week)	0.42 (0.09)	0.42 (0.09)	0.42 (0.09)	-1.035	0.301
Gestational weight gain				6.412	0.041

Insufficient	2115	1204 (26.69)	911 (28.58)		
Appropriate	3144	1894 (41.99)	1250 (39.21)		
Excessive	2440	1413 (31.32)	1027 (32.21)		
Prenatal visits	11.95 (3.25)	11.98 (3.27)	11.90 (3.23)	0.892	0.373
Prenatal visits				8.175	0.004
<8	824	521 (11.55)	303 (9.50)		
≥8	6875	3990 (88.45)	2885 (90.50)		
Total	7699	4511 (58.59)	3188 (41.41)		

Missing data: occupation, 26 (0.34%); education, 14 (0.18%); history of induced abortion, 2 (0.03%); and family history of chronic disease, 59 (0.77%).

Table 2 Pregnancy outcomes before and during the COVID-19 pandemic

Prevalence of outcomes (%)	Pre-COVID-19 (%)	COVID-19 (%)	χ^2	*P*
Adverse maternal outcomes				
Gestational diabetes[b]	1262 (27.99)	872 (27.38)	0.347	0.556
Gestational hypertension[b]	281 (6.23)	196 (6.15)	0.020	0.889
Premature rupture of membranes[b]	1385 (30.72)	1070 (33.59)	7.119	0.008
Caesarean section[b]	2065 (45.80)	1534 (48.16)	4.197	0.040
Adverse foetal outcomes				
Stillbirth	2 (0.04)	3 (0.09)	0.713	0.411[a]
Foetal distress[b]	527 (11.69)	418 (13.12)	3.574	0.059
Preterm birth[b]	199 (4.41)	121 (3.80)	1.767	0.184
Low birth weight[b]	137 (3.04)	96 (3.01)	0.004	0.951
Macrosomia[b]	304 (6.74)	213 (6.69)	0.009	0.925

Note: [a]Fisher exact test; [b]these pregnancy outcomes were all based on the data from 7694 live births.

Table 3 The influence of the COVID-19 pandemic on pregnancy outcomes

Pregnancy outcomes	Model A		Model B		Model C	
	cRR (95% CI)	P	aRR (95% CI)	P	aRR (95% CI)	P
Adverse maternal outcomes						
Gestational diabetes[b]	0.98 (0.91, 1.05)	0.556	0.97 (0.90, 1.05)	0.460	0.95 (0.88, 1.02)	0.136
Gestational hypertension[b]	0.99 (0.83, 1.18)	0.889	0.99 (0.83, 1.18)	0.920	0.96 (0.80, 1.14)	0.627
Premature rupture of membranes[b]	1.09 (1.02, 1.17)	0.007	1.10 (1.03, 1.17)	0.006	1.11 (1.04, 1.18)	0.003
Caesarean section[b]	1.05 (1.00, 1.10)	0.040	1.05 (1.00, 1.10)	0.055	1.05 (1.00, 1.10)	0.057
Adverse foetal outcomes						
Stillbirth	1.00 (1.00, 100)	0.427	1.00 (1.00, 1.00)	0.382	1.00 (1.00, 1.00)	0.387
Foetal distress[b]	1.12 (1.00, 1.27)	0.059	1.12 (1.00, 1.27)	0.061	1.14 (1.01, 1.29)	0.028
Preterm birth[b]	0.86 (0.69, 1.07)	0.184	0.84 (0.68, 1.05)	0.135	0.86 (0.69, 1.08)	0.190
Low birth weight[b]	0.99 (0.77, 1.28)	0.951	0.99 (0.77, 1.28)	0.954	1.00 (0.78, 1.30)	0.983
Macrosomia[b]	0.99 (0.84, 1.17)	0.925	1.00 (0.85, 1.19)	0.99	1.00(0.85, 1.19)	0.975

Note: cRR, crude risk ratio; aRR, adjusted risk ratio; [b]these pregnancy outcomes were all based on the data from 7694 live births.

Model A: a univariate model without controlling for any confounding factors;

Model B: controls for demographic characteristics (age, ethnicity, occupation, and education);

Model C: based on Model B, supplemented to control for gravidity, parity, history of miscarriage, history of induced abortion, pregnancy BMI, gestational weight gain, family history of chronic disease, and the number of prenatal visits.

Figure 1 Interrupted time-series analysis of the impact of COVID-19 on premature rupture of membranes

Figure 2 Interrupted time-series analysis of the impact of COVID-19 on foetal distress

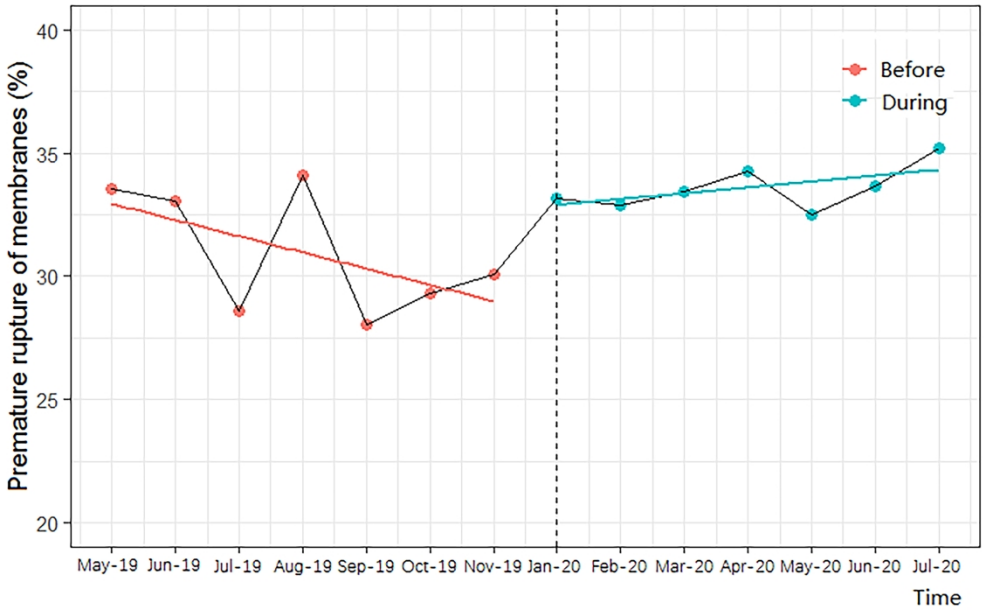


Figure 1 Interrupted time-series analysis of the impact of COVID-19 on premature rupture of membranes

194x122mm (300 x 300 DPI)

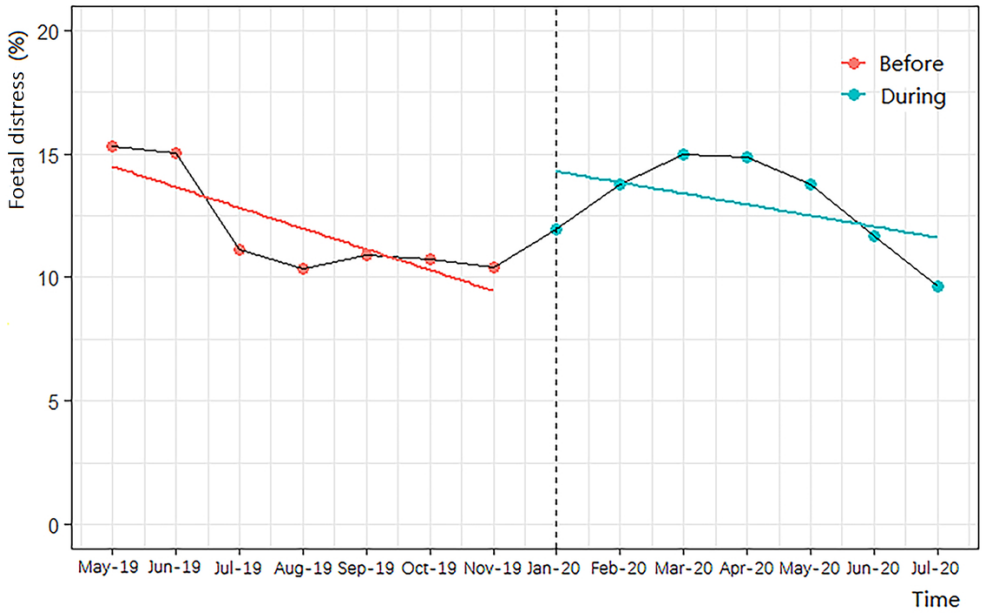
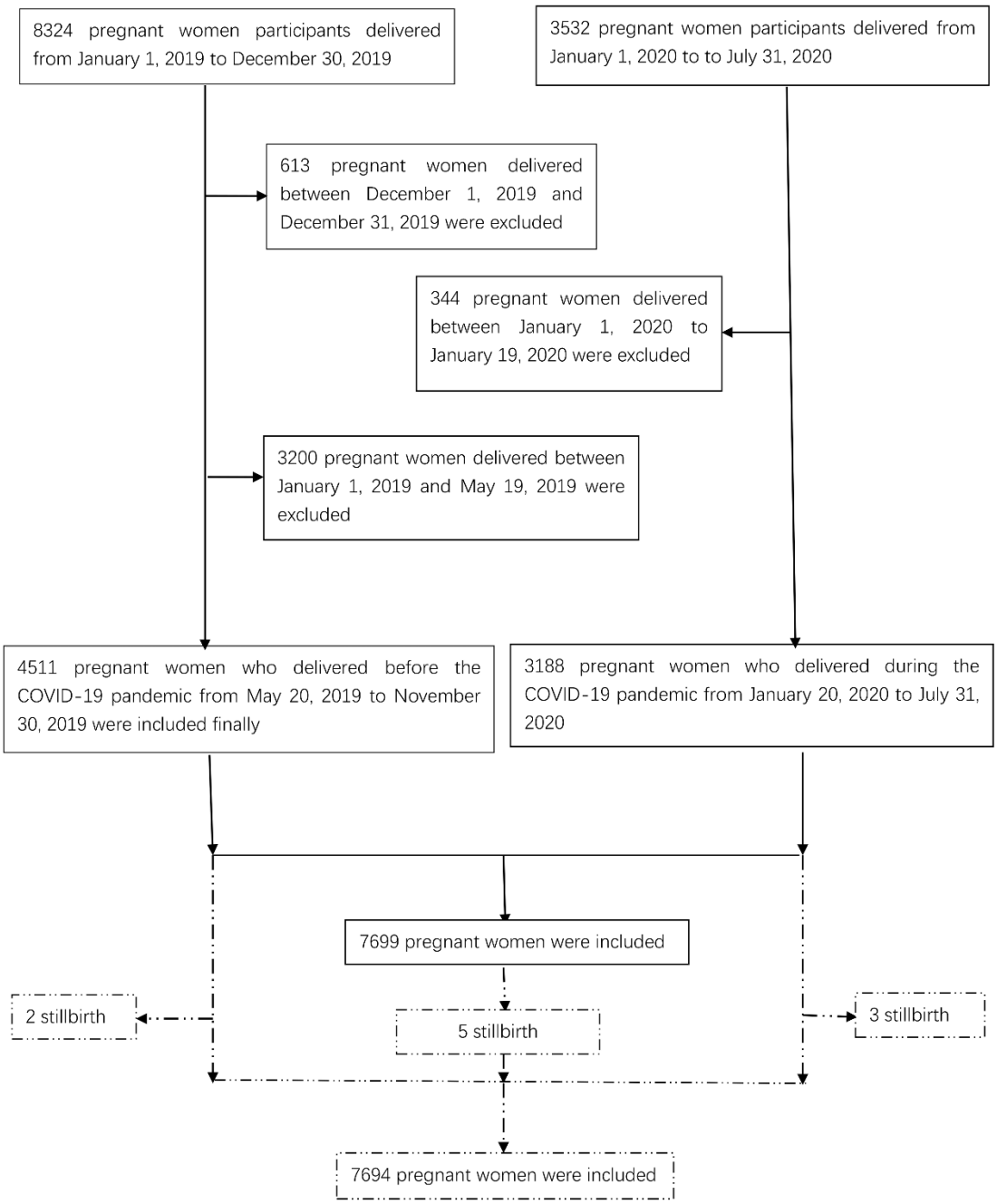


Figure 2 Interrupted time-series analysis of the impact of COVID-19 on foetal distress

97x61mm (300 x 300 DPI)



Supplemental Figure 1 The diagram of included and excluded participants

Supplemental Table 1 Characteristics of 7694 pregnant women before and during COVID-19 pandemic

Items	N / Mean (SD)	Pre COVID-19 (N,%; mean, SD)	COVID-19 (N,%; mean, SD)	χ^2/t	*P*
Maternal age (years)	30.20 (3.95)	30.01 (3.89)	30.45 (4.03)	-4.771	<0.0001
Maternal age (years)				8.301	0.016
⩽24	487 (6.33)	297 (6.59)	190 (5.97)		
25-35	6112 (79.44)	3612 (80.11)	2500 (78.49)		
⩾35	1095 (14.23)	600 (13.31)	495 (15.54)		
Ethnicity				0.024	0.876
Han	7222 (93.87)	4234 (93.90)	2988 (93.81)		
Other	472 (6.13)	275 (6.10)	197 (6.19)		
Occupation				0.13	0.677
Unemployed	910 (11.87)	528 (11.74)	382 (12.05)		
Employed	6758 (88.13)	3970 (88.26)	2788 (87.95)		
Education				7.683	0.053
Primary school or less	33 (0.43)	21 (0.47)	12 (0.38)		
Junior high school	578 (7.53)	355 (7.88)	223 (7.02)		
Senior high school	3772 (49.11)	2251 (49.97)	1521 (47.91)		
Undergraduate or above	3297 (42.93)	1878 (41.69)	1419 (44,69)		
Gravidity	2.01 (1.10)	2.01 (1.13)	2.01 (1.07)	0.165	0.869
Gravidity				1.988	0.370
1	3067 (39.86)	1809 (40.12)	1258 (39.50)		
2	2522 (32.78)	1450 (32.16)	1072 (33.66)		
⩾3	2105 (27.36)	1250 (27.72)	855 (26.84)		
Parity	0.45 (0.53)	0.44 (0.53)	0.46 (0.54)	-1.178	0.239
Parity				1.370	0.504
1	3191 (41.47)	1847 (40.96)	1344 (42.20)		
2	119 (1.55)	68 (1.51)	51 (1.60)		
⩾3	4384 (56.98)	2594 (57.53)	1790 (56.20)		
History of miscarriage	0.08 (0.32)	0.08 (0.31)	0.09 (0.32)	-0.955	0.339
History of miscarriage	579 (7.72)	328 (7.27)	251 (7.88)	0.986	0.321
History of induced abortion	0.47 (0.77)	0.48 (0.78)	0.45 (0.76)	1.334	0.182
History of induced abortion	2598 (33.78)	1558 (34.57)	1040 (32.65)	3.061	0.080
Family history of chronic disease	927 (12.14)	480 (10.72)	447 (14.16)	20.540	<0.001
Pre-pregnancy BMI, kg/m^2	22.24 (3.33)	22.22 (3.30)	22.27 (3.36)	-0.564	0.573
Pre-pregnancy BMI, kg/m^2				2.467	0.481
Underweight (18.5)	676 (8.79)	392 (8.69)	284 (8.92)		
Normal (18.5–24.9)	5714 (74.27)	3374 (74.83)	2340 (73.47)		
Overweight (25-29.9)	1077 (14.00)	609 (13.51)	468 (14.69)		
Obese (30)	227 (2.95)	134 (2.97)	93 (2.92)		
The rate of gestational weight gain (kg /week)	0.42 (0.09)	0.42 (0.09)	0.42 (0.09)	-1.044	0.297

Gestational weight gain				6.338	0.042
Insufficient	2112 (27.45)	1203 (26.68)	909 (28.54)		
Appropriate	3142 (40.84)	1893 (41.98)	1249 (39.22)		
Excessive	2440 (31.71)	1413 (31.34)	1027 (32.24)		
Prenatal visits	11.89 (3.37)	11.91 (3.43)	11.86 (3.27)	0.562	0.574
Prenatal visits				8.225	0.004
<8	822 (10.68)	520 (11.53)	302 (9.48)		
⩾8	6872 (89.32)	3989 (88.47)	2883 (90.52)		
Total	7694 (100)	4509 (58.60)	3185 (41.40)		

Missing data: occupation 26 (0.34%), education 14 (0.18%) history of induced abortion 2 (0.03%), and family history of chronic disease 59 (0.77%).

Supplemental Table 2 The influence of COVID-19 pandemic on pregnancy outcome

Pregnancy outcomes	Model C (full model)	
	aRR (95%CI)	P
Maternal adverse outcomes		
Gestational diabetes[b]	0.93 (0.87, 1.01)	0.066
Gestational hypertension[b]	0.94 (0.77, 1.14)	0.52
Premature rupture of membranes[b]	1.10 (1.03, 1.20)	0.007
Caesarean section[b]	1.04 (0.98, 1.10)	0.189
Fetal adverse outcomes		
Stillbirth	1.00 (1.00, 1.00)	0.647
Fetal distress[b]	1.14 (1.01, 1.28)	0.033
Preterm birth[b]	0.75 (0.56, 1.02)	0.063
Low birth weight[b]	0.87 (0.61, 1.24)	0.441
Macrosomia[b]	1.05 (0.87, 1.26)	0.608

Note：aRR, adjusted risk ratio; b these pregnancy outcomes all based on 7694 live birth data. Model C: controlling maternal age, ethnicity, occupation, education, gravidity, parity, history of miscarriage, history of induced abortion, pregnancy BMI, the rate of gestational weight gain, family history of chronic disease, the number of prenatal visit.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	4-5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047900.R2
Article Type:	Original research
Date Submitted by the Author:	11-Feb-2021
Complete List of Authors:	Du, Min; Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China Yang, Jie; Maternal and Child Health Hospital of Tongzhou District, Beijing, China. Han, Na; Maternal and Child Health Hospital of Tongzhou District, Beijing, China. Liu, Min ; Peking University, School of Public Health, Department of Epidemiology & Biostatistics Liu, Jue; Peking University School of Public Health, Department of Epidemiology & Biostatistics; Peking University Health Science Centre, National Health Commission Key Laboratory of Reproductive Health
Primary Subject Heading:	Public health
Secondary Subject Heading:	Public health, Epidemiology, Infectious diseases, Obstetrics and gynaecology
Keywords:	COVID-19, Public health < INFECTIOUS DISEASES, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title Page

Title: Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

Authors: Min Du[1*], Jie Yang[2*], Na Han[2], Min Liu[1], Jue Liu[1,3]

[*]Contributed equally.

Running title: COVID-19 pandemic and pregnancy outcome

Affiliations:

[1] Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China

[2] Maternal and Child Health Hospital of Tongzhou District, Beijing, China

[3] National Health Commission Key Laboratory of Reproductive Health, Peking University Health Science Center

Address correspondence to: Dr. Jue Liu, Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China.

E-mail address: jueliu@bjmu.edu.cn

Association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes: a cohort study

ABSTRACT

Objectives The secondary impacts of the COVID-19 pandemic on adverse maternal and neonatal outcomes remain unclear. In this study, we aimed to evaluate the association between the COVID-19 pandemic and the risk for adverse pregnancy outcomes.

Design We conduced retrospective analyses on 2 cohorts comprising 7699 pregnant women in Beijing, China, and compared pregnancy outcomes between the pre-COVID-2019 cohort (women who delivered from May 20, 2019 to November 30, 2019) and the COVID-2019 cohort (women who delivered from January 20, 2020 to July 31, 2020). The secondary impacts of the COVID-2019 pandemic on pregnancy outcomes were assessed by using multivariate log-binomial regression models, and we used interrupted time-series regression (ITS) analysis to further control the effects of time-trends.

Setting One tertiary-level centre in Beijing, China

Participants 7699 pregnant women.

Results Compared with women in the pre-COVID-19 pandemic group, pregnant women during the COVID-2019 pandemic were more likely to be of advanced age, exhibit insufficient or excessive gestational weight gain, and show a family history of chronic disease (all $P<0.05$). After controlling for other confounding factors, the risk of premature rupture of membranes and foetal distress was increased by 11% (95% CI, 1.04, 1.18; $p < 0.01$) and 14% (95% CI, 1.01, 1.29; $p < 0.05$), respectively, during the COVID-2019 pandemic. The association still remained in the ITS analysis after additionally controlling for time-trends (all $P<0.01$). We uncovered no other associations between the COVID-19 pandemic and other pregnancy outcomes ($P >0.05$).

Conclusions During the COVID-19 pandemic, more women manifested either insufficient or excessive gestational weight gain; and the risk of premature rupture of membranes and foetal distress was also higher during the pandemic.

Keywords: COVID-19, pregnancy outcome, cohort study

Strengths and limitations of this study

A major strength of this study was our estimation of the secondary impacts of the COVID-19 pandemic on adverse maternal and neonatal outcomes in China, the first such study of its kind.

We collected materials from the hospital-information system, which assured the accuracy of our data.

This study was of a retrospective nature and thus did not include physical exercise, diet, or psychological status, which might also be related to pregnancy outcomes.

The follow-up period in this study was only until delivery, such that the long-term impacts of the COVID-19 pandemic on women and their infants could not be explored.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has developed into the largest and deadliest pandemic respiratory disease. As of August 23, 2020, a total of 23,057,288 cases and 800,906 deaths have been reported to the World Health Organization (WHO). Perinatal research on COVID-19 is now primarily focused on pregnancy outcomes of women infected with SARS-CoV-2—including caesarean section[1,2], foetal distress[1], preterm birth[3], and even maternal death[4]. However, the adverse secondary impacts of the COVID-19 pandemic on maternal and neonatal outcomes remain unknown.

Several investigators have explored the effects of the COVID-19 pandemic on the mental health of pregnant women[5-8]. Ahorsu et al. found that the fear of COVID-19 was associated with depression, suicidal intention, adverse mental-health effects, and diminished overall quality of life among pregnant women[5]. Some studies showed that the COVID-19 pandemic was associated with obstetric care[9-12]—including institutional deliveries, high-risk pregnancy[9], intrapartum foetal heart rate monitoring, breastfeeding within 1 h of birth[10], and prenatal diagnosis/screening tests; while others have shown an effect of the pandemic on causing adverse maternal and neonatal outcomes[9,10,13-15]. The COVID-19 pandemic was associated with higher percentages of gestational hypertension[13,14], gestational diabetes[14], and premature rupture of membranes[15]. Goyal et al. reported that there was an increased rate of admission to the intensive care unit for pregnant women during the pandemic, compared with prior to COVID-19[9]. Ashish et al. also found that both

the rate of institutional stillbirth and institutional neonatal mortality increased significantly during the lockdown period in Nepal[10].

However, a majority of investigators [9,10,13-15] have only compared the rate of adverse maternal and neonatal outcomes between the pre-COVID-19 period and the COVID-19 pandemic period without controlling important factors related to adverse pregnancy outcomes (e.g., parity, gestational weight gain, or a family history of chronic disease). Thus, it is evident that more research is needed regarding the effects of the pandemic on some specific adverse outcomes, including caesarean section, foetal distress, low birth weight, and macrosomia. Unfortunately, in none of the previously aforementioned studies was there an examination of the association between the COVID-19 pandemic and adverse pregnancy outcomes in mainland China.

Therefore, we aimed in the present study to evaluate the secondary impacts of the COVID-19 pandemic on the risk of adverse pregnancy outcomes, using two cohorts (a pre-COVID-19 cohort and a COVID-19 cohort) to provide evidence for the implementation of targeted strategies that promote maternal and infant health during the COVID-19 pandemic.

METHODS

Study population

Two retrospective cohorts (pre-COVID-19 and during COVID-19) were analysed in this study, using the following inclusion criteria: (1) women with singleton pregnancies, (2) pregnant women who made prenatal visits to the Maternal and Child Health Hospital of Tongzhou District in Beijing, and (3) women who delivered between 2019 and July 31, 2020.

There were 8324 pregnant women who gave birth between January 1, 2019 and December 31, 2019; and 3532 pregnant women who gave birth between January 1, 2020 and July 31, 2020. Although we herein focused on the overall effects of the COVID-19 pandemic, none of the participants was infected with SARS-CoV-2 (the virus that causes *COVID-19*), given that the first case in China was reported in December 2019 and the first case in Beijing was reported in January 2020. To better assess the influence of the COVID-19 pandemic locally, we excluded the 613 participants who delivered during December 2019; the 344 women who delivered between January 1, 2020 and January 19, 2020; and also, the 3202 pregnant women who delivered between January 1, 2019 and May 19, 2019. Because we decided to only make close temporal comparisons

in order to avoid certain potentially confounding factors (e.g., differing policies between 2019 and 2020), we chose women who delivered from May 20, 2019 to November 30, 2019 as the pre-COVID-19 cohort; and those who delivered from January 20, 2020 to July 31, 2020 as the COVID-19 cohort. We thus included 4511 pregnant women in the pre-COVID-19 cohort and 3188 pregnant women in the COVID-19 cohort. However, in order to estimate the effects of the COVID-19 pandemic on other pregnancy outcomes (e.g., preterm birth and low birth weight), we excluded two stillbirths in the pre-COVID-19 cohort and three stillbirths in the COVID-19 cohort. We therefore ultimately included 4509 pregnant women who gave birth prior to the COVID-19 pandemic and 3185 pregnant women who gave birth during the COVID-19 pandemic (supplemental Figure 1 and supplemental Table 1). This study was approved by the Institutional Review Boards at Peking University (IRB00001052-18003).

Data collection

Data were collected from the hospital-information system, including basic demographic characteristics (age, ethnicity, occupation, and education), pregnancy status (gravidity, parity, history of miscarriage, and history of induced abortion), health status (pre-pregnancy body mass index [BMI]), gestational weight gain, a family history of chronic disease, and the number of prenatal visits. Of these characteristics, pre-pregnancy BMI was categorized based on the WHO cut-off points; gestational weight gain was calculated as the difference between weight at the last routine pregnancy visit and the pre-pregnancy weight; and the rate of gestational weight gain was calculated as the gestational weight gain/the gestational weeks at the last routine pregnancy visit. Categorization was in accordance with IOM criteria: gestational weight gain was classified as insufficient, appropriate, or excessive[16]; and a family history of chronic disease was principally with respect to whether the maternal parents or maternal grandparents manifested cardiovascular diseases such as heart disease and diabetes. The number of prenatal visits was not fewer than 8 times per year as recommended by the WHO[17].

Assessment of pregnancy outcomes

For this study we obtained information on pregnancy outcomes according to the ICD codes of discharge diagnosis, including gestational hypertension, gestational diabetes (GDM), premature rupture of membranes, delivery mode, stillbirth, foetal distress, preterm birth, low birth weight, and macrosomia. Preterm birth was defined as less than 37 weeks of gestation based on the

interval between the last menstrual period and the date of delivery of the baby. Delivery mode was categorized as either caesarean section or vaginal delivery. Caesarean section included both medical and psychosocial indications, and vaginal delivery included spontaneous vaginal and assisted vaginal births. Infant birth weight was divided into low birth weight (< 2500 g) and macrosomia (> 4000 g).

Statistical analyses

We compared the characteristics of women before and during the COVID-19 pandemic by using the χ^2 or *t* test. The χ^2 test was also used to compare pregnancy outcomes of women before and during the pandemic. Given that odds ratios (ORs) cannot provide accurate estimates for the relative risks (RRs) in the cohort studies, we used univariate and multivariate log-binomial regression models to estimate the crude risk ratios (cRRs) and adjusted risk ratios (aRRs) of the impacts of the COVID-19 pandemic on adverse pregnancy outcomes using the SAS Software Package V.9.4, (SAS Institute). We also calculated the attributable risk percentage (AR%, 95% CI). We performed sensitivity analysis by fitting different models to examine the robustness of the estimation, and 3 models were fitted. The first (model A) was unadjusted; the second (model B) was adjusted for baseline demographic characteristics (maternal age, ethnicity, occupation, education); and the third model (full-model C) was further adjusted for pregnancy condition (gravidity, parity, history of miscarriage, history of induced abortion) and health status (pre-pregnancy BMI, gestational weight gain [GWG], family history of chronic disease, and the number of prenatal visits). We additionally added a full-model C by replacing categorical variables with continuous variables, including maternal age, gravidity, parity, history of miscarriage, history of induced abortion, pre-pregnancy BMI, the rate of gestational weight gain, and the number of prenatal visits. Since interrupted time-series regression (ITS) analysis is useful for evaluating population-level health interventions with a clearly defined point in time [18], we conducted ITS to examine the impacts of COVID-19 on pregnancy outcomes using R 3.4.2 (R-team)[18]. A 2-sided value of $P<0.05$ was considered to be statistically significant for all of the analyses.

Patient and Public Involvement

No patients were involved in this anonymous data set.

RESULTS

A total of 7699 women were included in this study, with a mean age of 30.07 (±3.98, SD) and an average gestational week of 38.90 (± 1.46) weeks; 93.87% were of Han ethnicity, 11.83% were unemployed, and 56.97% had a bachelor's degree or less. Characteristics of the study population are provided in **Table 1**. Compared with women in the pre-COVID-19 pandemic group, pregnant women during the COVID-19 pandemic were more likely to be of advanced age (15.53% vs. 13.30%, respectively), show insufficient (28.58% vs. 26.69%) or excessive gestational weight gain (32.21% vs. 31.32%), have a family history of chronic disease (14.18% vs 10.74%), and have ⩾8 prenatal visits (9.50% vs. 11.55%, respectively; all *P*<0.05). Other characteristics were not significantly different between the two groups (all *P*>0.05).

The prevalences of caesarean sections and premature rupture of membranes were higher during the COVID-19 pandemic period compared with women prior to the pandemic (48.16% vs. 45.80%, *P*=0.040; and 33.59% vs. 30.72%, respectively; *P*=0.008). However, the prevalences of other pregnancy outcomes were not significantly different during the COVID-19 pandemic compared with the pre-pandemic period (*P*>0.05, **Table 2**).

In our log-binomial regression models, and after adjusting for all confounding factors, the risk for premature rupture of membranes and foetal distress during the COVID-19 pandemic compared to pre-COVID-19 women was increased by 11% (95% CI, 1.04, 1.18; p < 0.01) and 14% (95% CI, 1.01, 1.29; p < 0.05), respectively (**Table 3**). Additionally, the attributable risk percentage of the COVID-19 pandemic on premature rupture of membranes was 9.91 (95% CI, 3.84, 15.25), and the attributable risk percentage of the pandemic on foetal distress was 12.28 (95% CI, 0.99, 22.48). However, we uncovered no other associations between the COVID-19 pandemic and other pregnancy outcomes, and demonstrated similar results for the additional full-model C (as shown in supplemental Table 2). After controlling for time-trends in the interrupted time-series regression, the COVID-19 pandemic was still associated with an increased risk of premature rupture of membranes (*P*<0.001, Figure **1**) and foetal distress (*P*<0.01, Figure **2**).

DISCUSSION

Summary of the findings

To the best of our knowledge, this is the first cohort study to focus on secondary impacts of the COVID-19 pandemic on pregnancy outcomes in mainland China. Herein, we showed that more

pregnant women were of advanced age, with abnormal gestational weight gain, and a family history of chronic disease during the COVID-19 pandemic. The risks of premature rupture of membranes and foetal distress among pregnant women who gave birth during the COVID-19 pandemic were also higher than in those women who gave birth before the pandemic.

Strengths and limitations

The strengths of this study included its cohort-study design and use of well-established methods to detect the impacts of the COVID-19 pandemic on pregnancy outcomes, and we thus included two cohorts (a pre-COVID-19 cohort and a COVID-19 cohort), using the same study site. In addition, using log-binomial regression models and interrupted time-series analysis, we were able to evaluate the impact of a policy change or natural intervention (such as a pandemic).

There were some limitations to our study. First, this study was a retrospective study. We did not collect data on physical exercise, diet, or psychological status, which might also be related to pregnancy outcomes. The follow-up period for this study was only up to delivery, such that long-term impacts of the COVID-19 pandemic on women and their infants could not be explored. Second, this is a single-centre cohort study, and we only included participants at 1 hospital in Beijing. Therefore, these results may have limited relevance to other health-care systems outside of Beijing. Larger and multi-centre prospective cohort studies are therefore needed in the future to confirm and clarify the findings of our study. Finally, due to the lack of specific individual obstetric-management records, we could not investigate the impacts of specific measures on pregnancy outcomes.

Comparison with other studies

Although researchers had previously found that the prevalence of premature rupture of membranes in pregnant women infected with the novel coronavirus was relatively high[2,19-21], few had explored the secondary impacts of the COVID-19 pandemic on this adverse pregnancy outcome. Kugelman et al. found that there was a higher proportion of women who had premature rupture of membranes in a COVID-19 cohort (20.6% vs. 11.0%, p<0.001)[15]; and in the present study, we also found that the proportion of women who presented with premature rupture of membranes was higher in the COVID-19 cohort (33.59% vs. 30.72%, *P*=0.008). Compared to women pre-COVID-19, we observed that the risk of premature rupture of membranes during the COVID-19 pandemic was increased by 11% (95% CI, 1.04, 1.18; p < 0.01).

Premature rupture of membranes may additionally be associated with increased maternal anxiety during the COVID-19 pandemic[6,7]. Studies have shown that as the severity of the pandemic increased, the level of anxiety among pregnant women also increased [22]; and that maternal anxiety and depression were associated with premature rupture of membranes[23] because of the decreased levels of creatinine and choline[24] and an altered diurnal pattern of cortisol (manifested as a flattened cortisol decline and higher evening cortisol) [25,26]. We also found that the risk of foetal distress was increased during the pandemic, but noted a general lack of published research on this topic. The association might be related to enhanced psychological, neuroendocrine, and neurochemical changes caused by social-isolation stress during the COVID-19 pandemic[27]. Many countries took measures to control the transmission of the virus by keeping social distance (e.g., stay-at-home orders, the cancellation of public events, lockdown), which may increase the risk of social-isolation stress for pregnant women[27]. In one study, it was reported that one-third of women underwent an inadequate number of antenatal visits because of the lockdown for fear of contracting infection, resulting in 44.7% of pregnancies showing complications[9]. In addition, women pregnant during the COVID-19 pandemic might not have visited the hospital as frequently as in a non-pandemic time, which might have led to under instruction in perinatal healthcare and inadequate receipt of routine medical services[28]. However, the specific mechanism(s) underlying the effects on pregnancy of the COVID-19 pandemic remains unclear. In order to reduce the impact of COVID-19 pandemic on psychological health and increase the usage of perinatal healthcare for pregnant women during the pandemic, the National Health Commission of China launched a new notice on February 8, 2020 that proposed strengthening health counselling, screening, and follow-ups for pregnant women[29]. Besides, local hospital had tried their best to ensure the access to prenatal care by taking comprehensive measures (e.g., online appointment service, online consultation work, outpatient service and so on) to minimize the influence of COVID-19 pandemic on pregnancy and medical services. Nevertheless, our study showed that the secondary impacts of COVID-19 on pregnant women should draw greater attention, especially with respect to the premature rupture of membranes and foetal distress.

In our study, the prevalence of caesarean sections among pregnant women experiencing the COVID-19-pandemic was higher than in the group prior to the pandemic, which may be related to the higher proportions of caesarean-section indices that included foetal distress. We also found

that there was a greater proportion of women aged ≥35 years in the COVID-19 cohort, and that this cohort contained more women with a family history of chronic disease. This might be related to the implementation of the two-child policy since 2016 in China that more women with advanced maternal age were willing to have babies[30]. Zhao et al. found that the percentages of older pregnant women increased significantly in 2017 and 2018 compared with numbers in 2014, 2015 and 2016[31]. A steadily increased proportion of pregnant women with advanced age has been observed in recent years [32]. Correspondingly, family members of old pregnant women were more likely to have a history of chronic diseases. What's more, the impact of second-child policy might be greater in 2020 than that in 2019 due to the policies of isolation in home and travel restrictions. Kugelman et al. also found that women visited the obstetrical emergency department at a more advanced mean gestational age during the pandemic outbreak, compared with the pre-COVID period[15]. Pregnant women who visit outpatient clinics should also be followed as often as possible, and the psychological and emotional states of these women should be assessed and monitored in follow-up visits to address the possible risks of adverse pregnancy complications and outcomes[33].

Implications for clinicians and policymakers

Pregnant women should be considered as key populations in strategies focusing on management during COVID-19 pandemic. Service provision during the epidemic is needed to ensure the early identification and intervention of high-risk pregnant women. *To ensure the access to prenatal care, hospitals should take comprehensive and case-by-case measures, assess and monitor the risk of adverse pregnancy outcomes in follow-up visits as often as possible.[33] Additionally, apart from healthcare services, pregnant women should be educated about the importance of regular prenatal visits, healthy lifestyle and measures to prevent infection (wearing masks, hand hygiene, etc.) during the COVID-19 pandemic. More attention should be paid to reduce the indirect impact of COVID-19 pandemic on vulnerable pregnant women. Additionally, large multi-centre cohort studies should be conducted in future to further explore the long-term impact and the mechanism of COVID-19 pandemic on pregnant women and their babies to ensure maternal and child health.*

CONCLUSIONS

In summary, we found that there were more pregnant women with abnormal gestational weight gain during the COVID-19 pandemic. The risk for premature rupture of membranes and foetal distress in pregnant women during the pandemic was also higher than in pregnant women before

the COVID-19 pandemic. Our findings highlight the importance of improved management during pregnancy to reduce adverse maternal and infant outcomes, especially with respect to premature rupture of membranes and foetal distress. Cohort studies are needed to assess the long-term direct and indirect impact of COVID-19 pandemic on maternal and child health in the future.

Contributors All the authors have made substantial contributions to the conception, design of the work; or the acquisition, analysis, or interpretation of data for the work. They have participated in drafting the manuscript and approval of the version to be published. Conceptualization: Jue Liu. Methodology: Jue Liu, Min Liu. Investigation: Min Du, Jie Yang, Jue Liu. Data acquisition: Jie Yang, Na Han. Data Curation: Min Du, Jie Yang, Jue Liu. Data analysis: Min Du, Jie Yang. Preparation of tables and figures: Min Du. Initial draft of manuscript: Min Du, Jie Yang, Jue Liu. Writing – Review & Editing: Na Han, Min Liu, Jue Liu. Supervision: Jue Liu.

Funding This research was funded by the National Natural Science Foundation of China (grant number 81703240), the National Science and Technology Key Projects on Prevention and Treatment of Major Infectious Diseases of China (grant number 2020ZX10001002), and the National Key Research and Development Project of China (grant number 2020YFC0846300).

Competing interests All authors report no conflict of interest.

Patient consent for publication Not required.

Ethics approval This study was approved by the Institutional Review Boards at Peking University (IRB00001052-18003).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request to the corresponding author.

REFERENCE

1 Gao YJ, Ye L, Zhang JS, et al. Clinical features and outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2020;20:564.

2 Zhang L, Dong L, Ming L, et al. Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection during late pregnancy: a report of 18 patients from Wuhan, China. BMC Pregnancy Childbirth. 2020;20:394.

3 Lokken EM, Walker CL, Delaney S, et al. Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington State [published online ahead of print, 2020 May 19]. Am J Obstet Gynecol. 2020;S0002-9378(20)30558-5.

4 Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. Am J Obstet Gynecol. 2020;223:109.e1-109.e16.

5 Ahorsu DK, Imani V, Lin CY, et al. Associations Between Fear of COVID-19, Mental Health, and Preventive Behaviours Across Pregnant Women and Husbands: An Actor-Partner Interdependence Modelling [published online ahead of print, 2020 Jun 11]. Int J Ment Health Addict. 2020;1-15. doi:10.1007/s11469-020-00340-x6.

6 Berthelot N, Lemieux R, Garon-Bissonnette J, et al. Uptrend in distress and psychiatric symptomatology in pregnant women during the coronavirus disease 2019 pandemic. Acta Obstet Gynecol Scand. 2020;99:848-855.

7 Hessami K, Romanelli C, Chiurazzi M, Cozzolino M. COVID-19 pandemic and maternal mental health: a systematic review and meta-analysis [published online ahead of print, 2020 Nov 1]. J Matern Fetal Neonatal Med. 2020;1-8. doi:10.1080/14767058.2020.1843155

8 Lemieux R, Garon-Bissonnette J, Loiselle M, Martel É, Drouin-Maziade C, Berthelot N. Association entre la fréquence de consultation des médias d'information et la détresse psychologique chez les femmes enceintes durant la pandémie de COVID-19: Association between news media consulting frequency and psychological distress in pregnant women during the COVID-19 pandemic [published online ahead of print, 2020 Oct 21]. Can J Psychiatry. 2020;706743720963917. doi:10.1177/0706743720963917

9 Goyal M, Singh P, Singh K, Shekhar S, Agrawal N, Misra S. The effect of the COVID-19 pandemic on maternal health due to delay in seeking health care: Experience from a tertiary center [published online ahead of print, 2020 Oct 31]. Int J Gynaecol Obstet. 2020;10.1002/ijgo.13457. doi:10.1002/ijgo.13457

10 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. doi:10.1016/S2214-109X(20)30345-4

11 Lalaguna Mallada P, Díaz-Gómez NM, Costa Romero M, San Feliciano Martín L, Gabarrell Guiu C. Impacto de la pandemia de Covid-19 en la lactancia y cuidados al nacimiento. Importancia de recuperar las buenas prácticas [The impact of Covid-19 pandemic on breastfeeding and birth care. The importance of recovering good practices.]. Rev Esp Salud Publica. 2020;94:e202007083. Published 2020 Jul 9.12.

12 Ozalp M, Demir O, Akbas H, Kaya E, Celik C, Osmanagaoglu MA. Effect of COVID-19 pandemic process on prenatal diagnostic procedures [published online ahead of print, 2020 Sep 1]. J Matern Fetal Neonatal Med. 2020;1-6. doi:10.1080/14767058.2020.1815190

13 Gu XX, Chen K, Yu H, Liang GY, Chen H, Shen Y. How to prevent in-hospital COVID-19 infection and reassure women about the safety of pregnancy: Experience from an obstetric center in China. J Int Med Res. 2020;48(7):300060520939337.doi:10.1177/0300060520939337
14 Justman N, Shahak G, Gutzeit O, et al. Lockdown with a Price: The impact of the COVID-19 Pandemic on Prenatal Care and Perinatal Outcomes in a Tertiary Care Center. Isr Med Assoc J. 2020;22(9):533-537.
15 Kugelman N, Lavie O, Assaf W, et al. Changes in the obstetrical emergency department profile during the COVID-19 pandemic [published online ahead of print, 2020 Nov 16]. J Matern Fetal Neonatal Med. 2020;1-7. doi:10.1080/14767058.2020.1847072
16 Institute of Medicine and National Research Council. Weight Gain during Pregnancy: Reexamining the Guidelines. In: Washington, DC:The National Academies Press; 2009:240-255.
17 WHO recommendations on antenatal care for a positive pregnancy experience. Published 2016. Accessed [Available from: www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/.]
18 Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46:348-355.
19 Xu S, Shao F, Bao B, et al. Clinical Manifestation and Neonatal Outcomes of Pregnant Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. Open Forum Infect Dis. 2020;7(7):ofaa283. Published 2020 Jul 5. doi:10.1093/ofid/ofaa283
20 Chen Y, Bai J. Maternal and infant outcomes of full-term pregnancy combined with COVID-2019 in Wuhan, China: retrospective case series. Arch Gynecol Obstet. 2020;302(3):545-551. doi:10.1007/s00404-020-05573-8
21 Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. Int J Gynaecol Obstet. 2020;150(3):312-317. doi:10.1002/ijgo.13265
22 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. doi:10.1016/j.ejogrb.2020.04.022
23 Khanghah AG, Khalesi ZB, Hassanzadeh R Afagh. The importance of depression during pregnancy. JBRA Assist Reprod. 2020;24(4):405-410. Published 2020 Oct 6. doi:10.5935/1518-0557.20200010
24 Wu Y, Lu YC, Jacobs M, et al. Association of Prenatal Maternal Psychological Distress With Fetal Brain Growth, Metabolism, and Cortical Maturation. JAMA Netw Open. 2020;3(1):e1919940. Published 2020 Jan 3. doi:10.1001/jamanetworkopen.2019.19940
25 Nabi G, Siddique R, Xiaoyan W, et al. COVID-19 induced psychosocial stressors during gestation: possible maternal and neonatal consequences. Curr Med Res Opin. 2020;36(10):1633-1634. doi:10.1080/03007995.2020.1815003
26 Gilles M, Otto H, Wolf IAC, et al. Maternal hypothalamus-pituitary-adrenal (HPA) system activity and stress during pregnancy: Effects on gestational age and infant's anthropometric measures at birth. Psychoneuroendocrinology. 2018;94:152-161. doi:10.1016/j.psyneuen.2018.04.022 27.

27 Wang L, Nabi G, Zhang T, Wu Y, Li D. Potential Neurochemical and Neuroendocrine Effects of Social Distancing Amidst the COVID-19 Pandemic. Front Endocrinol (Lausanne). 2020;11:582288. Published 2020 Oct 8. doi:10.3389/fendo.2020.582288

28 Coxon K, Turienzo CF, Kweekel L, et al. The impact of the coronavirus (COVID-19) pandemic on maternity care in Europe. Midwifery. 2020;88:102779. doi:10.1016/j.midw.2020.102779

29 National Health Commission of the People's Republic of China. Notice on strengthening maternal disease treatment and safe midwifery during the prevention and control of new coronavirus pneumonia. (accessed Feb 8, 2020) [Available from: http://www.nhc.gov.cn/xcs/zhengcwj/202002/4f80657b346e4d6ba76e2cfc3888c630.]

30 Liu J, Liu M, Zhang S, Ma Q, Wang Q. Intent to have a second child among Chinese women of childbearing age following China's new universal two-child policy a cross-sectional study. BMJ Sex Reprod Health 2019;46(1):59-66. doi:10.1136/bmjsrh-2018-200197.

31 Zhao F, Xu Y, Chen YT, Cheng JY, Pan XY. Influence of the universal two-child policy on obstetric issues. Eur J Obstet Gynecol Reprod Biol. 2020;252:479-482. doi:10.1016/j.ejogrb.2020.07.028

32 Liu J, Song L, Qiu J, Jing W, Wang L, Dai Y, Qin G, Liu M. Reducing maternal mortality in China in the era of the two-child policy. BMJ Glob Health. 2020;5(2):e002157. doi: 10.1136/bmjgh-2019-002157.

33 Vivanti AJ, Deruelle P, Picone O, et al. Follow-up for pregnant women during the COVID-19 pandemic: French national authority for health recommendations. J Gynecol Obstet Hum Reprod. 2020;49(7):101804. doi:10.1016/j.jogoh.2020.101804

Table 1 Characteristics of 7699 pregnant women before and during the COVID-19 pandemic

Items	N / Mean (SD)	Pre COVID-19 (N,%; mean, SD)	COVID-19 (N,%; mean, SD)	χ^2/t	*P*
Maternal age (years)	30.07 (3.98)	29.92 (3.91)	30.29 (4.08)	-3.42	0.001
Maternal age (years)				8.262	0.016
≤24	487	297 (6.58)	190 (5.96)		
25-35	6117	3614 (80.12)	2503 (78.51)		
≥35	1095	600 (13.30)	495 (15.53)		
Ethnicity					
Han	7227	4236 (93.90)	2991 (93.82)	0.022	0.881
Other	472	275 (6.10)	197 (6.18)		
Occupation				0.202	0.653
Unemployed	911	528 (11.73)	383 (12.07)		
Employed	6762	3972 (88.27)	2790 (87.93)		
Education				7.782	0.051
Primary school or less	34	22 (0.49)	12 (0.38)		
Junior high school	578	355 (7.88)	223 (7.02)		
Senior high school	3774	2251 (49.94)	1523 (47.92)		
Undergraduate or above	3299	1879 (41.69)	1420 (44.68)		
Gravidity	1.99 (1.08)	1.99 (1.07)	2.00 (1.08)	-0.223	0.823
Gravidity				1.883	0.39
1	3068	1809 (40.10)	1259 (39.49)		
2	2523	1451 (32.17)	1072 (33.63)		
≥3	2108	1251 (27.73)	857 (26.88)		
Parity	0.43 (0.53)	0.43 (0.52)	0.44 (0.54)	-0.815	0.415
Parity				1.362	0.506
1	3195	1849 (40.99)	1346 (42.22)		
2	119	68 (1.51)	51 (1.60)		
≥3	4385	2594 (57.50)	1791 (56.18)		
History of miscarriage	0.09 (0.32)	0.08 (0.32)	0.09 (0.33)	-1.18	0.239
History of miscarriage	579	328 (7.27)	251 (7.87)	0.974	0.324
History of induced abortion	0.47 (0.76)	0.48 (0.76)	0.46 (0.76)	0.88	0.379
History of induced abortion	2601	1559 (34.58)	1042 (32.69)	2.982	0.084
Family history of chronic disease	929	481 (10.74)	448 (14.18)	20.536	<0.0001
Pre-pregnancy BMI, kg/m^2	22.04 (3.12)	22.09 (3.17)	21.97 (3.17)	1.45	0.147
Pre-pregnancy BMI, kg/m^2				2.465	0.482
Underweight (18.5)	676	392 (8.69)	284 (8.91)		
Normal (18.5–24.9)	5717	3375 (74.82)	2342 (73.46)		
Overweight (25-29.9)	1079	610 (13.52)	469 (14.71)		
Obese (30)	227	134 (2.97)	93 (2.92)		
The rate of gestational weight gain (kg /week)	0.42 (0.09)	0.42 (0.09)	0.42 (0.09)	-1.035	0.301
Gestational weight gain				6.412	0.041

Insufficient	2115	1204 (26.69)	911 (28.58)		
Appropriate	3144	1894 (41.99)	1250 (39.21)		
Excessive	2440	1413 (31.32)	1027 (32.21)		
Prenatal visits	11.95 (3.25)	11.98 (3.27)	11.90 (3.23)	0.892	0.373
Prenatal visits				8.175	0.004
<8	824	521 (11.55)	303 (9.50)		
≥8	6875	3990 (88.45)	2885 (90.50)		
Total	7699	4511 (58.59)	3188 (41.41)		

Missing data: occupation, 26 (0.34%); education, 14 (0.18%); history of induced abortion, 2 (0.03%); and family history of chronic disease, 59 (0.77%).

Table 2 Pregnancy outcomes before and during the COVID-19 pandemic

Prevalence of outcomes (%)	Pre-COVID-19 (%)	COVID-19 (%)	χ^2	*P*
Adverse maternal outcomes				
Gestational diabetes[b]	1262 (27.99)	872 (27.38)	0.347	0.556
Gestational hypertension[b]	281 (6.23)	196 (6.15)	0.020	0.889
Premature rupture of membranes[b]	1385 (30.72)	1070 (33.59)	7.119	0.008
Caesarean section[b]	2065 (45.80)	1534 (48.16)	4.197	0.040
Adverse foetal outcomes				
Stillbirth	2 (0.04)	3 (0.09)	0.713	0.411[a]
Foetal distress[b]	527 (11.69)	418 (13.12)	3.574	0.059
Preterm birth[b]	199 (4.41)	121 (3.80)	1.767	0.184
Low birth weight[b]	137 (3.04)	96 (3.01)	0.004	0.951
Macrosomia[b]	304 (6.74)	213 (6.69)	0.009	0.925

Note: [a]Fisher exact test; [b]these pregnancy outcomes were all based on the data from 7694 live births.

Table 3 The influence of the COVID-19 pandemic on pregnancy outcomes

Pregnancy outcomes	Model A		Model B		Model C	
	cRR (95% CI)	P	aRR (95% CI)	P	aRR (95% CI)	P
Adverse maternal outcomes						
Gestational diabetes[b]	0.98 (0.91, 1.05)	0.556	0.97 (0.90, 1.05)	0.460	0.95 (0.88, 1.02)	0.136
Gestational hypertension[b]	0.99 (0.83, 1.18)	0.889	0.99 (0.83, 1.18)	0.920	0.96 (0.80, 1.14)	0.627
Premature rupture of membranes[b]	1.09 (1.02, 1.17)	0.007	1.10 (1.03, 1.17)	0.006	1.11 (1.04, 1.18)	0.003
Caesarean section[b]	1.05 (1.00, 1.10)	0.040	1.05 (1.00, 1.10)	0.055	1.05 (1.00, 1.10)	0.057
Adverse foetal outcomes						
Stillbirth	1.00 (1.00, 100)	0.427	1.00 (1.00, 1.00)	0.382	1.00 (1.00, 1.00)	0.387
Foetal distress[b]	1.12 (1.00, 1.27)	0.059	1.12 (1.00, 1.27)	0.061	1.14 (1.01, 1.29)	0.028
Preterm birth[b]	0.86 (0.69, 1.07)	0.184	0.84 (0.68, 1.05)	0.135	0.86 (0.69, 1.08)	0.190
Low birth weight[b]	0.99 (0.77, 1.28)	0.951	0.99 (0.77, 1.28)	0.954	1.00 (0.78, 1.30)	0.983
Macrosomia[b]	0.99 (0.84, 1.17)	0.925	1.00 (0.85, 1.19)	0.99	1.00(0.85, 1.19)	0.975

Note: cRR, crude risk ratio; aRR, adjusted risk ratio; [b]these pregnancy outcomes were all based on the data from 7694 live births.

Model A: a univariate model without controlling for any confounding factors;

Model B: controls for demographic characteristics (age, ethnicity, occupation, and education);

Model C: based on Model B, supplemented to control for gravidity, parity, history of miscarriage, history of induced abortion, pregnancy BMI, gestational weight gain, family history of chronic disease, and the number of prenatal visits.

Figure 1 Interrupted time-series analysis of the impact of COVID-19 on premature rupture of membranes

Figure 2 Interrupted time-series analysis of the impact of COVID-19 on foetal distress

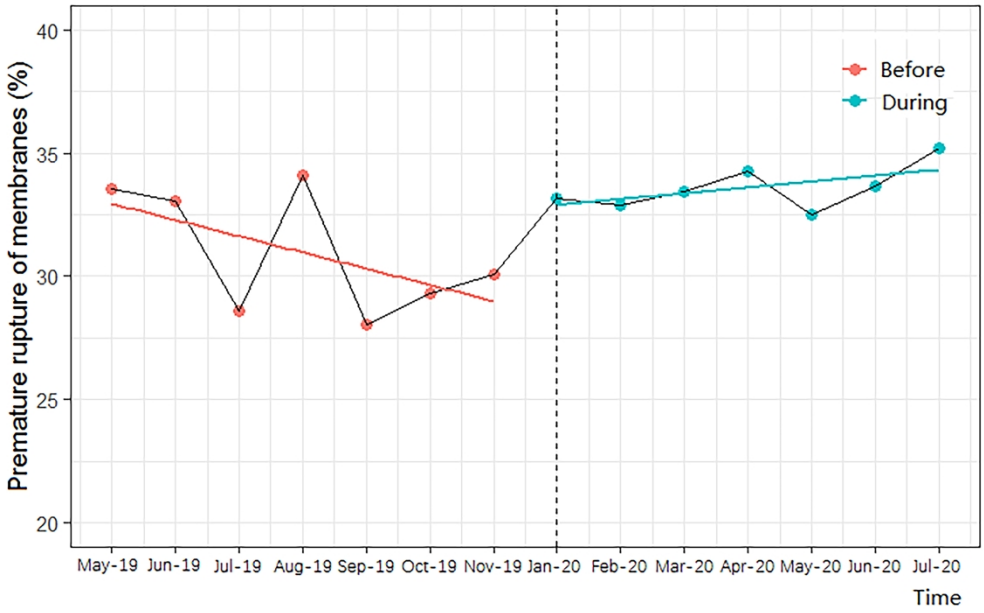


Figure 1 Interrupted time-series analysis of the impact of COVID-19 on premature rupture of membranes

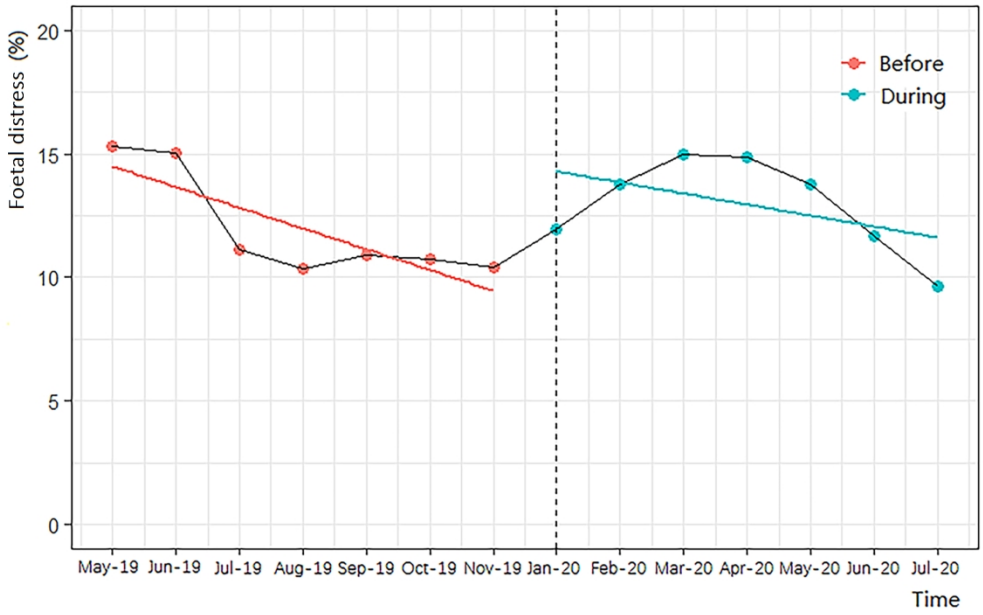
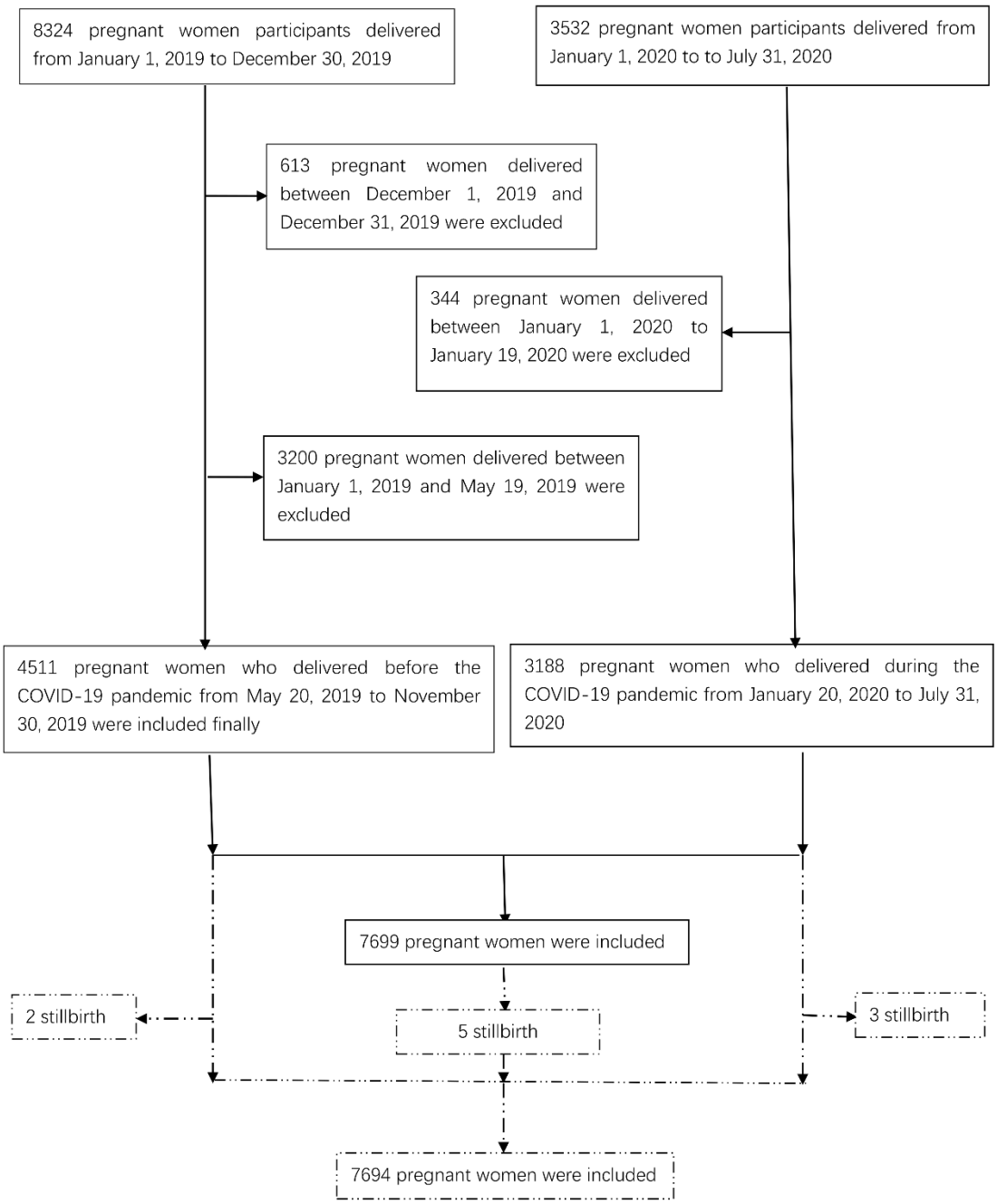


Figure 2 Interrupted time-series analysis of the impact of COVID-19 on foetal distress

97x61mm (500 x 500 DPI)



Supplemental Figure 1 The diagram of included and excluded participants

Supplemental Table 1 Characteristics of 7694 pregnant women before and during COVID-19 pandemic

Items	N / Mean (SD)	Pre COVID-19 (N,%; mean, SD)	COVID-19 (N,%; mean, SD)	χ^2/t	*P*
Maternal age (years)	30.20 (3.95)	30.01 (3.89)	30.45 (4.03)	-4.771	<0.0001
Maternal age (years)				8.301	0.016
⩽24	487 (6.33)	297 (6.59)	190 (5.97)		
25-35	6112 (79.44)	3612 (80.11)	2500 (78.49)		
⩾35	1095 (14.23)	600 (13.31)	495 (15.54)		
Ethnicity				0.024	0.876
Han	7222 (93.87)	4234 (93.90)	2988 (93.81)		
Other	472 (6.13)	275 (6.10)	197 (6.19)		
Occupation				0.13	0.677
Unemployed	910 (11.87)	528 (11.74)	382 (12.05)		
Employed	6758 (88.13)	3970 (88.26)	2788 (87.95)		
Education				7.683	0.053
Primary school or less	33 (0.43)	21 (0.47)	12 (0.38)		
Junior high school	578 (7.53)	355 (7.88)	223 (7.02)		
Senior high school	3772 (49.11)	2251 (49.97)	1521 (47.91)		
Undergraduate or above	3297 (42.93)	1878 (41.69)	1419 (44,69)		
Gravidity	2.01 (1.10)	2.01 (1.13)	2.01 (1.07)	0.165	0.869
Gravidity				1.988	0.370
1	3067 (39.86)	1809 (40.12)	1258 (39.50)		
2	2522 (32.78)	1450 (32.16)	1072 (33.66)		
⩾3	2105 (27.36)	1250 (27.72)	855 (26.84)		
Parity	0.45 (0.53)	0.44 (0.53)	0.46 (0.54)	-1.178	0.239
Parity				1.370	0.504
1	3191 (41.47)	1847 (40.96)	1344 (42.20)		
2	119 (1.55)	68 (1.51)	51 (1.60)		
⩾3	4384 (56.98)	2594 (57.53)	1790 (56.20)		
History of miscarriage	0.08 (0.32)	0.08 (0.31)	0.09 (0.32)	-0.955	0.339
History of miscarriage	579 (7.72)	328 (7.27)	251 (7.88)	0.986	0.321
History of induced abortion	0.47 (0.77)	0.48 (0.78)	0.45 (0.76)	1.334	0.182
History of induced abortion	2598 (33.78)	1558 (34.57)	1040 (32.65)	3.061	0.080
Family history of chronic disease	927 (12.14)	480 (10.72)	447 (14.16)	20.540	<0.001
Pre-pregnancy BMI, kg/m^2	22.24 (3.33)	22.22 (3.30)	22.27 (3.36)	-0.564	0.573
Pre-pregnancy BMI, kg/m^2				2.467	0.481
Underweight (18.5)	676 (8.79)	392 (8.69)	284 (8.92)		
Normal (18.5–24.9)	5714 (74.27)	3374 (74.83)	2340 (73.47)		
Overweight (25-29.9)	1077 (14.00)	609 (13.51)	468 (14.69)		
Obese (30)	227 (2.95)	134 (2.97)	93 (2.92)		
The rate of gestational weight gain (kg /week)	0.42 (0.09)	0.42 (0.09)	0.42 (0.09)	-1.044	0.297

Gestational weight gain				6.338	0.042
Insufficient	2112 (27.45)	1203 (26.68)	909 (28.54)		
Appropriate	3142 (40.84)	1893 (41.98)	1249 (39.22)		
Excessive	2440 (31.71)	1413 (31.34)	1027 (32.24)		
Prenatal visits	11.89 (3.37)	11.91 (3.43)	11.86 (3.27)	0.562	0.574
Prenatal visits				8.225	0.004
<8	822 (10.68)	520 (11.53)	302 (9.48)		
⩾8	6872 (89.32)	3989 (88.47)	2883 (90.52)		
Total	7694 (100)	4509 (58.60)	3185 (41.40)		

Missing data: occupation 26 (0.34%), education 14 (0.18%) history of induced abortion 2 (0.03%), and family history of chronic disease 59 (0.77%).

Supplemental Table 2 The influence of COVID-19 pandemic on pregnancy outcome

Pregnancy outcomes	Model C (full model)	
	aRR (95%CI)	P
Maternal adverse outcomes		
Gestational diabetes[b]	0.93 (0.87, 1.01)	0.066
Gestational hypertension[b]	0.94 (0.77, 1.14)	0.52
Premature rupture of membranes[b]	1.10 (1.03, 1.20)	0.007
Caesarean section[b]	1.04 (0.98, 1.10)	0.189
Fetal adverse outcomes		
Stillbirth	1.00 (1.00, 1.00)	0.647
Fetal distress[b]	1.14 (1.01, 1.28)	0.033
Preterm birth[b]	0.75 (0.56, 1.02)	0.063
Low birth weight[b]	0.87 (0.61, 1.24)	0.441
Macrosomia[b]	1.05 (0.87, 1.26)	0.608

Note：aRR, adjusted risk ratio; b these pregnancy outcomes all based on 7694 live birth data. Model C: controlling maternal age, ethnicity, occupation, education, gravidity, parity, history of miscarriage, history of induced abortion, pregnancy BMI, the rate of gestational weight gain, family history of chronic disease, the number of prenatal visit.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	4-5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.