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Association of interpregnancy interval and risk of adverse pregnancy outcomes in woman by different previous gestational ages

Peiran Chen[1], Yi Mu[1], Zheng Liu[1], Yanping Wang[1], Xiaohong Li[1], Li Dai[1], Qi Li[1], Mingrong Li[1], Yanxia Xie[1], Juan Liang[1,2], Jun Zhu[1,3]

[1]National Office for Maternal and Child Health Surveillance of China, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610066, China;

[2]Department of Obstetrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610066, China;

[3]Key Laboratory of Birth Defects and Related Diseases of Women and Children, Ministry of Education, Sichuan University, Chengdu, Sichuan 610066, China.

Abstract

Background: With an increasing proportion of multiparas, proper interpregnancy intervals (IPIs) are urgently needed. However, the association between IPIs and adverse perinatal outcomes has always been debated. This study aimed to explore the association between IPIs and adverse outcomes in different fertility policy periods and for different previous gestational ages.

Methods: We used individual data from China's National Maternal Near Miss Surveillance System between 2014 and 2019. Multivariable Poisson models with restricted cubic splines were used. Each adverse outcome was analyzed separately in the overall model and stratified models. The stratified models included different categories of fertility policy periods (2014–2015, 2016–2017, and 2018–2019) and infant gestational age in previous pregnancy (<28 weeks, 28–36 weeks, and ≥37 weeks).

Results: There were 781,731 pregnancies enrolled in this study. A short IPI (≤6 months) was associated with an increased risk of preterm birth (OR [95% CI]: 1.63 [1.55, 1.71] for vaginal delivery [VD] and 1.10 [1.03, 1.19] for cesarean section [CS]), low Apgar scores and small for gestational age (SGA), and a decreased risk of diabetes mellitus in pregnancy, preeclampsia or eclampsia, and gestational hypertension. A long IPI (≥60 months) was associated with an increased risk of preterm birth (OR [95% CI]: 1.18 [1.11, 1.26] for VD and 1.39 [1.32, 1.47] for CS), placenta previa, postpartum hemorrhage, diabetes mellitus in pregnancy, preeclampsia or eclampsia, and gestational hypertension. Fertility policy changes had little effect on the association of IPIs and adverse maternal and neonatal outcomes. The estimated risk of preterm birth, low Apgar scores, SGA, diabetes mellitus in pregnancy, and gestational hypertension was more profound among women with previous term births than among those with preterm births or pregnancy loss.

Conclusion: For pregnant women with shorter or longer IPIs, more targeted health care measures during pregnancy should be formulated according to infant gestational age in previous pregnancy.

Keywords: Interpregnancy interval; Fertility policy; Gestational age; Preterm birth; Gestational hypertension; Diabetes mellitus in pregnancy

Introduction

The interpregnancy interval (IPI) was thought to be a modifiable factor to prevent adverse effects on perinatal and maternal health in subsequent pregnancies. The World Health Organization (WHO) suggested that at least 2 years of birth spacing and 6 months of postabortion spacing could reduce the risk of adverse maternal, perinatal, and infant outcomes.[1] However, previous research based on a population study showed that pregnant women have the lowest risk of adverse perinatal outcomes, such as low birthweight, preterm birth, and small for gestational age (SGA), at an IPI of 18–23 months after a previous live birth.[2] Shorter intervals (less than 6 months) are associated with an increased risk of low birthweight, preterm birth, SGA, stillbirth, and early neonatal death.[2–6] A longer interval (longer than 4 years) may increase the risk of preeclampsia recurrence.[7] The "maternal nutritional depletion" hypothesis demonstrating inadequate recovery from previous pregnancy was thought to be a mechanism of the association between a short interbirth interval (month gap between two consecutive live births) and increased adverse neonatal outcomes.[8,9] Moreover, some researchers believe that the effect of the IPI is confounded by maternal health status and social, economic, and demographic factors.[10,11] However, fully controlling for all possible confounding factors is difficult to carry out in one study.

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Correspondence to: Juan Liang, Department of Obstetrics, West China Second University Hospital, Sichuan University; National Office for Maternal and Child Health Surveillance of China, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610066, China
E-Mail: liangjuan@scu.edu.cn

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To date, most relevant studies have been published in developed countries, with little research performed in developing countries. Thus, the applicability of previous research conclusions to developing countries is unclear. With the gradual relaxation of China's fertility policy at the end of 2013 and the introduction of the "universal two-child" policy in 2016, the proportion of second children has increased.[12] Although some research about the association of IPIs and adverse outcomes in Chinese women has been published, all these studies were partial studies from a province or a particular level of hospitals without adequate representativeness of China. All these studies included IPIs as a categorical variable without an adequate scientific or clinical basis. In addition, most of these studies focused on adverse neonatal outcomes. Little is known about adverse maternal outcomes.[4,13–16]

A baby boom was observed shortly after the "universal two-child" policy, and this increase in births was assumed to be driven by the fertility policy change.[17] We noticed that previous studies have analyzed the association between IPIs and adverse outcomes after pregnancy loss. However, the adverse outcomes were mainly restricted to recurrent miscarriage and abortion, and due to insufficient research, the conclusion is controversial.[9,18–20] In addition, we also found a study that compared the risk of preterm birth in women with long and short IPIs among those with previous preterm births and term births. However, this study was conducted in high-income countries.[21] The conclusion may not be suitable for developing countries that are restricted by health care services. In addition, the effect of previous gestational age on other adverse health outcomes is unknown. Thus, we built models stratified by infant gestational age in previous pregnancy to further explore the associations between IPIs and adverse maternal and prenatal outcomes.

Methods

Ethical approval

This study was approved by the Ethics Committee of the West China Second University Hospital (No. 2012008).

Data collection

Individual maternal data were collected through China's National Maternal Near Miss Surveillance System (NMNMSS) from January 2010 to December 2019. The NMNMSS was first established in 2010. Currently, it covers 441 member hospitals that manage more than 1000 deliveries annually. Since there is no National Maternal Near Miss surveillance hospital in Tibet, the included member hospitals were located in 326 districts or counties throughout 30 provinces, autonomous regions and municipalities in Chinese mainland. Quality control was performed for all the collected data at the provincial, municipal, and county levels at least four times a year.[22] Data collected by this system have been used in many studies that focused on Chinese maternal and neonatal health.[23–25] The NMNMSS collects the sociodemographic and obstetric information of pregnant and postpartum women from the obstetric departments of surveillance hospitals. The collected data include the name and code of the hospital, the date of delivery, the number of antenatal visits, maternal educational level and marital status, maternal age, delivery mode, fetal sex, parity, and the number of fetuses. The sampling strategy, data collection, and quality control procedure have been detailed elsewhere.[22,24,26] The analyzed population who had identical ID numbers, had at least two consecutive singleton pregnancy records, and became pregnant again between 2014 and 2019 were included.

Definition

The IPI was defined as the gap in months between the end of a pregnancy (including abortion, stillbirth, or live birth) and the date of the last menstrual period of the subsequent pregnancy.

We categorized the analyzed time period into three phases: the "selective one-child" policy period, the "universal two-child" policy period, and the "cooling-off" period, which were defined as 2014–2015 (Phase 1), 2016–2017 (Phase 2), and 2018–2019 (Phase 3). The "universal two-child" policy began in January 2016,[27] allowing every couple to have a second child. Thus, we set the first time point as January 2016. After the relaxation of the "universal two-child" policy, the national birth rate peaked in 2016, reaching 12.95‰. However, the national birth rate fell from 12.43‰ in 2017 to 10.94‰ in 2018, as the Statistical Bulletin reported.[28,29] We inferred that the birth rate change may have been driven by the fact that a proportion of women who were not permitted to have a second child before the relaxation of the second child policy gave birth intensively during 2016 and 2017. However, the incentive of the fertility policy was temporary. After that time, the enthusiasm of the two-child policy entered the cooling-off period as the birth rate decreased. Thus, the second time point was set at January 2018.

In addition, we also wanted to explore factors at the individual level. As for the different recommended IPIs after live birth and abortion, we categorized infant gestational age in previous pregnancy preceding the interval as <28 weeks, 28–36 weeks, and ≥37 weeks.

Perinatal outcomes, including preterm birth by cesarean section (CS), preterm birth by vaginal delivery (VD), low Apgar scores, SGA, and large for gestational age (LGA), were defined through different inclusion and exclusion criteria. As the information for the onset of labor was inaccessible in this research, we stratified preterm birth by different delivery modes, such as preterm birth (VD) and preterm birth (CS). Details of the criteria are listed in Supplementary Table 1, http://links.lww.com/CM9/B661.[30,31] Gestational age in China is generally ascertained based on the last menstrual period or the ultrasound examination when the date of the last menstrual period is not known.[26]

Maternal outcomes focused on some of the most common maternal complications in China, including placenta previa, postpartum hemorrhage, gestational hypertension, preeclampsia or eclampsia, and diabetes mellitus in pregnancy. Postpartum hemorrhage, including soft birth canal lacerations, uterine atony, retained placenta, or other postpartum hemorrhage, was defined as an obstetric hemorrhage greater than 500 mL during VD or 1000 mL during CS and occurring in or after the third stage of labor.[32] Gestational hypertension was defined as new-onset hypertension (≥140/90 mmHg) after 20 weeks of gestation with the normalization of blood pressure at 12 weeks postpartum. Preeclampsia was defined as hypertension (≥140/90 mmHg) and proteinuria after 20 weeks of gestation or hypertension plus the involvement of one organ or system in women with previously normal blood pressure. Eclampsia was diagnosed as the presence of new-onset grand mal seizures in women with preeclampsia.[33] Since women usually do not receive screening for diabetes mellitus before pregnancy, it can be challenging to distinguish gestational diabetes mellitus from pre-existing diabetes. However, gestational diabetes mellitus took account of approximately 90% of diabetes mellitus in pregnancy.[34,35] Thus, we defined diabetes mellitus in pregnancy in this research, which refers to pre-existing diabetes mellitus and diabetes mellitus arising in pregnancy.

Other variables, including region, prenatal examination, maternal educational level, maternal marital status, maternal age, previous delivery mode, parity, and pregnancy loss (including stillbirth and early neonatal death; fetuses with unknown birth vital signs and a gestational age less than 28 weeks were also classified as pregnancy loss) in previous pregnancy, were used as covariates. Based on the hospital's location, we defined the region as urban and rural. The hospital level (from level 1 to level 3) was certified by the administrative department of health. It was classified according to the number of beds, categories of clinical departments, numbers of medical personnel, type and quantity of equipment, and hospital funding, with level 3 hospitals providing more advanced care. All covariates were measured at the time of the previous delivery preceding the birth interval.

Statistical analysis

The IPI was used as a continuous variable. To estimate the risk of adverse health outcomes at each IPI, an IPI of 24 months was used as the reference.[4,5,36]

To assess the impact of fertility policy changes on IPIs, a single-group design with multiple treatment periods interrupted time series analysis (ITSA) was used.[37] The outcome was the IPI in months. The two time points (January 2016 and January 2018) were used as the start of the two treatment periods. Variables that may change over the years, including region (urban or rural), hospital level, prenatal examination, advanced maternal age, maternal education level, delivery mode in previous pregnancy, parity, pregnancy loss, and maternal complications in previous pregnancy, were used as covariates.

Poisson regression analysis is regarded as an appropriate approach to analyzing the risk of rare events. However, the error could be overestimated when estimating relative risk (RR) in binomial recorded outcomes. This can be overcome by employing a robust error variance procedure in Poisson regression models. Therefore, we performed a Poisson regression analysis with a robust variance estimator to examine the association between IPIs and perinatal or maternal outcomes. Crude and adjusted relative risks (aRRs) with 95% confidence intervals (CIs) were estimated separately. In the multivariable model, rural areas, hospital level, inadequate prenatal examination, fertility policy period, gestational age in previous pregnancy, maternal educational status, maternal age, delivery mode in previous pregnancy, parity, pregnant losses, maternal complication, interactions of fertility policy period category, and previous pregnancy category were used as covariates. Restricted cubic splines (RCSs) with five knots placed at the 5th, 25th, 50th, 75th, and 95th percentiles were also included in the model to allow non-linear assumptions between the IPIs and each adverse outcome. Each adverse outcome was analyzed in the overall model and stratified models separately. Because the relationship between IPIs and adverse neonatal and maternal outcomes might vary as a function of the change in the fertility policy period or length of a previous pregnancy, we analyzed the potential mediating effect of fertility policy changes or the length of a previous pregnancy by fitting a Poisson model using interactions of the fertility policy period category and previous pregnancy category in the overall model. The stratified models were carried out in different categories of fertility policy periods (2014–2015, 2016–2017, and 2018–2019) and infant gestational age in previous pregnancy (<28 weeks, 28–36 weeks, and ≥37 weeks). A test for interaction for each outcome at each interval length in separate subgroups was performed.[38]

Considering the possible collinearity between age and the IPI, we also conducted a sensitivity analysis that excluded adjustment for maternal age. Differences between the adjusted and unadjusted models for age were found to be minor. To assess the potential bias of unmeasured confounding variables, we also calculated the E value, which represents the minimum strength that unmeasured confounding needs to have on both IPIs and adverse perinatal and maternal outcomes to fully explain the observed association.[39] STATA (version 16.0; Stata Corp., TX, USA) and SAS (version 9.4; SAS Institute Inc., NC, USA) were used to conduct the analysis. P <0.05 (two-sided) were considered statistically significant.

Results

There were 781,731 pregnancies enrolled in this study. Approximately half of the pregnancies (51.86%) had an IPI less than 24 months. The enrolled women were mainly primiparas aged less than 30 years with an educational level of college or above. Women who were from urban areas, had adequate prenatal examinations, had a live singleton birth through CS, and did not have any maternal complications tended to have a longer IPI [Table 1]. The mean IPIs and their 95% CIs were 19.40 (19.33, 19.47) months, 26.66 (26.61, 26.71) months,

Table 1: Demographic characteristics of pregnancies in previous pregnancy according to categories of IPI (*n* = 781,731).

	IPIs, *n* (%)				
Characteristics	≤6 months	7–24 months	25–42 months	43–59 months	≥60 months
Total	42,626 (5.45)	362,769 (46.41)	225,289 (28.82)	102,026 (13.05)	49,021 (6.27)
Urban or rural areas					
Urban	14,687 (34.46)	151,014 (41.63)	109,797 (48.74)	53,072 (52.02)	25,732 (52.49)
Rural	27,939 (65.54)	211,755 (58.37)	115,492 (51.26)	48,954 (47.98)	23,289 (47.51)
Hospital level					
Level 1	6619 (15.53)	56,332 (15.53)	31,046 (13.78)	12,734 (12.48)	5994 (12.23)
Level 2	26,168 (61.39)	198,436 (54.70)	114,410 (50.78)	50,090 (49.10)	23,940 (48.84)
Level 3	9839 (23.08)	108,001 (29.77)	79,833 (35.44)	39,202 (38.42)	19,087 (38.94)
Maternal education					
College or above	33,543 (78.69)	253,388 (69.85)	142,406 (63.21)	61,157 (59.94)	29,956 (61.11)
Below college	8707 (20.43)	104,472 (28.80)	78,968 (35.05)	38,701 (37.93)	18,060 (36.84)
Unknown	376 (0.88)	4909 (1.35)	3915 (1.74)	2168 (2.12)	1005 (2.05)
Maternal age					
<25 years	18,276 (42.88)	135,710 (37.41)	72,343 (32.11)	32,000 (31.36)	16,227 (33.10)
25–29 years	16,670 (39.11)	166,653 (45.94)	114,757 (50.94)	53,970 (52.90)	25,696 (52.42)
30–34 years	5751 (13.49)	50,632 (13.96)	33,663 (14.94)	14,706 (14.41)	6709 (13.69)
≥35 years	1929 (4.53)	9774 (2.69)	4526 (2.01)	1350 (1.32)	389 (0.79)
Prenatal examination					
≥5 times	20,101 (47.16)	234,672 (64.69)	155,128 (68.86)	71,295 (69.88)	33,434 (68.20)
<5 times	21,476 (50.38)	119,701 (33.00)	64,518 (28.64)	28,332 (27.77)	14,519 (29.62)
Unknown	1049 (2.46)	8396 (2.31)	5643 (2.50)	2399 (2.35)	1068 (2.18)
Parity					
Primipara	29,418 (69.01)	284,888 (78.53)	186,311 (82.70)	86,382 (84.67)	41,768 (85.20)
Multipara	13,203 (30.97)	77,849 (21.46)	38,927 (17.28)	15,528 (15.22)	7188 (14.66)
Unknown	5 (0.01)	32 (0.01)	51 (0.02)	116 (0.11)	65 (0.13)
Previous delivery mode					
VD	40,007 (93.86)	289,254 (79.74)	137,359 (60.97)	57,042 (55.91)	26,347 (53.75)
Cesarean delivery	2617 (6.14)	73,503 (20.26)	87,922 (39.03)	44,977 (44.08)	22,672 (46.25)
Unknown	2 (<0.01)	12 (<0.01)	8 (<0.01)	7 (0.01)	2 (<0.01)
Pregnancy loss					
No	30,238 (70.94)	335,129 (92.38)	217,150 (96.39)	99,687 (97.71)	47,978 (97.87)
Yes	12,379 (29.04)	27,589 (7.61)	8110 (3.60)	2325 (2.28)	1031 (2.10)
Unknown	9 (0.02)	51 (0.01)	29 (0.01)	14 (0.01)	12 (0.02)
Maternal complication					
Yes	17,679 (41.47)	150,990 (41.62)	88,020 (39.07)	34,635 (33.95)	13,708 (27.96)
No	24,947 (58.53)	211,777 (58.38)	137,268 (60.93)	67,390 (66.05)	35,313 (72.04)
Unknown	0	2 (<0.01)	1 (<0.01)	1 (<0.01)	0
Fertility policy period					
2014–2015	14,236 (33.40)	102,822 (28.34)	44,546 (19.77)	2895 (2.84)	8 (0.02)
2016–2017	15,185 (35.62)	133,196 (36.72)	88,939 (39.48)	46,952 (46.02)	7822 (15.96)
2018–2019	13,205 (30.98)	126,751 (34.94)	91,804 (40.75)	52,179 (51.14)	41,191 (84.03)
Previous gestational age					
<28 weeks	10,588 (24.84)	22,708 (6.26)	6559 (2.91)	1911 (1.87)	833 (1.70)
28–36 weeks	3064 (7.19)	16,534 (4.56)	9617 (4.27)	4203 (4.12)	2055 (4.19)
≥37 weeks	28,974 (67.97)	323,527 (89.18)	209,113 (92.82)	95,912 (94.01)	46,133 (94.11)

IPIs: Interpregnancy intervals; VD: Vaginal delivery.

and 31.34 (31.29, 31.39) months for each fertility policy period [Supplementary Table 2, http://links.lww.com/CM9/B661]. The IPI increased significantly at the announcement of the fertility policy among primiparas [Supplementary Table 3, http://links.lww.com/CM9/B661]. The majority of women (90.01%) enrolled in our study became pregnant again after delivering a term infant. Women with infants with a longer previous gestational age tended to have a longer IPI before becoming pregnant again. After adjusting for covariates, the mean IPIs with their 95% CIs were 25.30 (24.98, 25.62) months, 27.13 (26.97, 27.29) months, and 27.19 (27.15, 27.23) months for previous gestational ages less than 28 weeks, 28–36 weeks, and greater than 37 weeks, respectively [Supplementary Table 4, http://links.lww.com/CM9/B661]. Overall, we found little notable difference in the association between different fertility policy periods and previous gestational age.

Regarding adverse neonatal outcomes, the risk of preterm birth (VD) and preterm birth (CS) changed in a "U" shape as the IPI increased (the RRs and their 95% CIs were 1.63 (1.55, 1.71) and 1.10 (1.03, 1.19) for a 6-month IPI, and 1.18 (1.11, 1.26) and 1.39 (1.32, 1.47) for a 60-month IPI). The risk of LGA and SGA exhibited an inverse correlation with increasing IPI. The risk of LGA increased from 0.77 (95% CI, 0.75, 0.79) to 1.13 (95% CI, 1.10, 1.15), while the risk of SGA decreased from 1.36 (95% CI, 1.32, 1.40) to 0.98 (95% CI, 0.94, 1.01) [Table 2]. A rare difference in adverse perinatal outcomes was observed in the fertility policy period stratified analysis [Figure 1, Supplementary Table 5, Figures 1 and 2, http://links.lww.com/CM9/B661]. In the previous gestational age stratified analysis, the increased risk of preterm birth (VD) and low Apgar scores in women with short IPIs was more profound among those who became pregnant again subsequent to a previous term birth. Women who become pregnant again after delivering an infant with a previous gestational age greater than 37 weeks had a notably higher risk of preterm birth (CS) than women with a previous gestational age less than 28 weeks in short IPIs [Figure 2, Supplementary Table 6, Figures 3 and 4, http://links.lww.com/CM9/B661].

Regarding adverse maternal outcomes, the risk of most of the adverse maternal outcomes increased with an increasing IPI, and the risk of preeclampsia or eclampsia increased from 0.68 (95% CI, 0.62, 0.75) to 2.16 (95% CI, 2.02, 2.32). However, the risk of uterine rupture was significantly higher at the 6-month interval (1.31 [95% CI, 1.08, 1.59]) [Table 2]. In the fertility policy period stratified analysis, rare notable differences in adverse maternal outcomes were observed in different categories of fertility phase periods [Figure 3, Supplementary Table 5, Figures 5 and 6, http://links.lww.com/CM9/B661]. In the previous gestational age stratified analysis, rare differences were observed in women with different IPIs among those who became pregnant after delivering an infant with a gestational age less than 28 weeks. The decreased risk of diabetes mellitus in pregnancy in women with short IPIs was more profound for those who became pregnant again after a term birth than for those who became pregnant again after delivering an infant with a gestational age less than 28 weeks or between 28 weeks and 36 weeks. The increased risk of gestational hypertension in women with long IPIs was higher for those who became pregnant again after a term birth than for those who became pregnant after a delivering an infant with a gestational age less than 28 weeks [Figure 4, Supplementary Table 6, Figures 7 and 8, http://links.lww.com/CM9/B661].

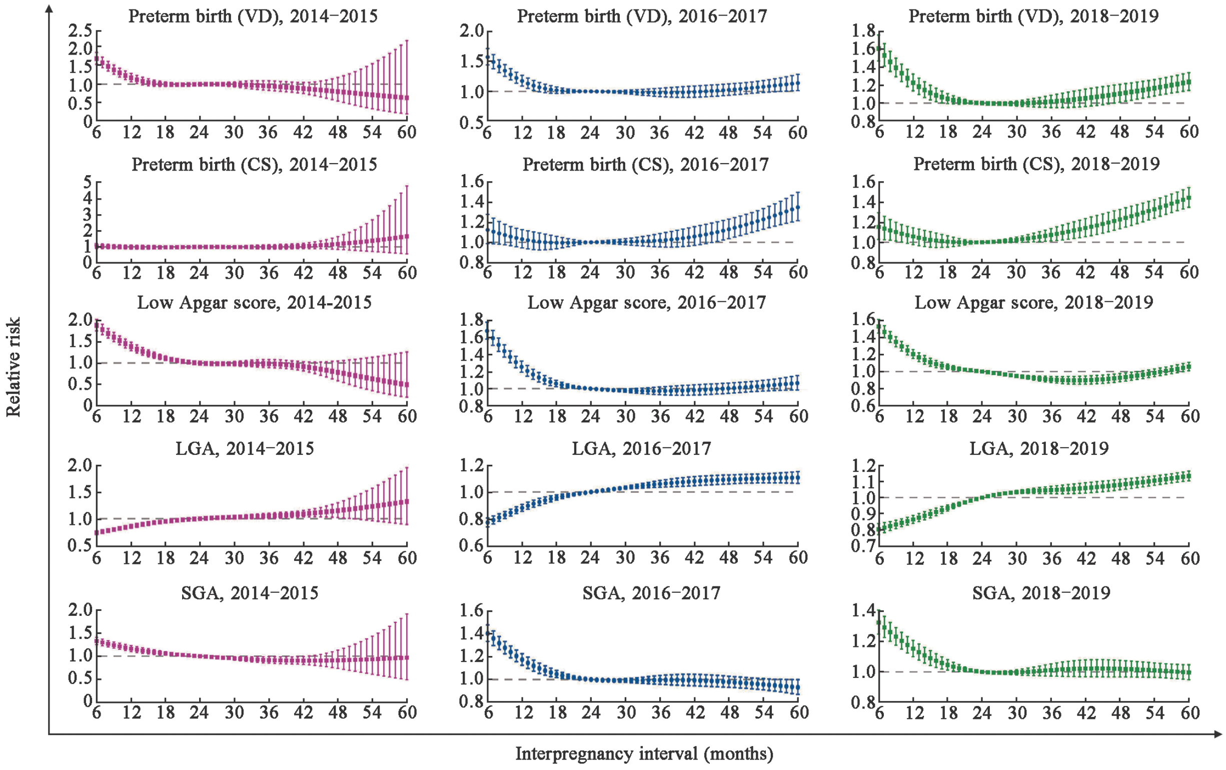

Figure 1: aRR of neonatal outcomes according to IPI stratified by fertility policy period. Adjusted for: urban or rural areas, hospital level, inadequate prenatal examination, gestational age in previous pregnancy, maternal educational status, maternal age, delivery mode in previous pregnancy, parity, pregnant losses, and maternal complication. aRR: Adjusted relative risk; CS: Cesarean section; IPI: Interpregnancy interval; LGA: Large for gestational age; SGA: Small for gestational age; VD: Vaginal delivery.

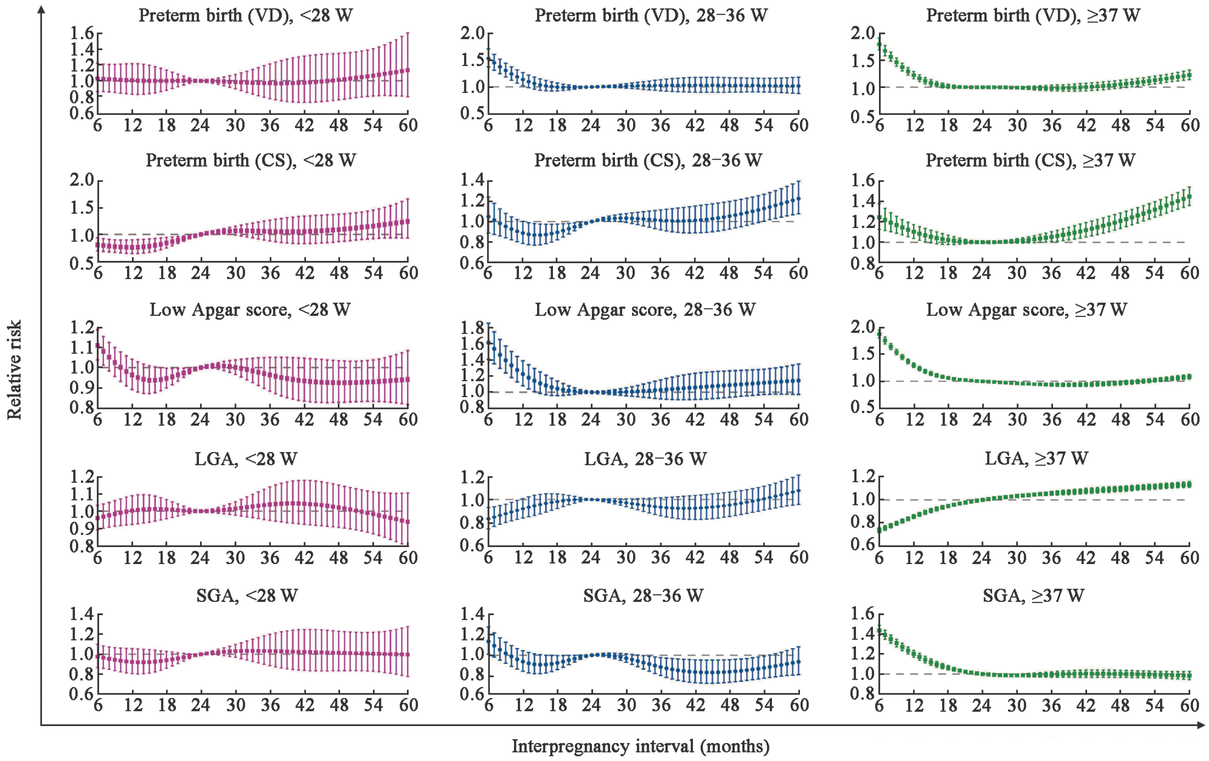

Figure 2: aRR of neonatal outcomes according to IPI stratified by gestational age in previous pregnancy. Adjusted for: urban or rural areas, hospital level, inadequate prenatal examination, fertility policy period, maternal educational status, maternal age, delivery mode in previous pregnancy, parity, pregnant losses, and maternal complication. aRR: Adjusted relative risk; CS: Cesarean section; IPI: Interpregnancy interval; LGA: Large for gestational age; SGA: Small for gestational age; VD: Vaginal delivery.

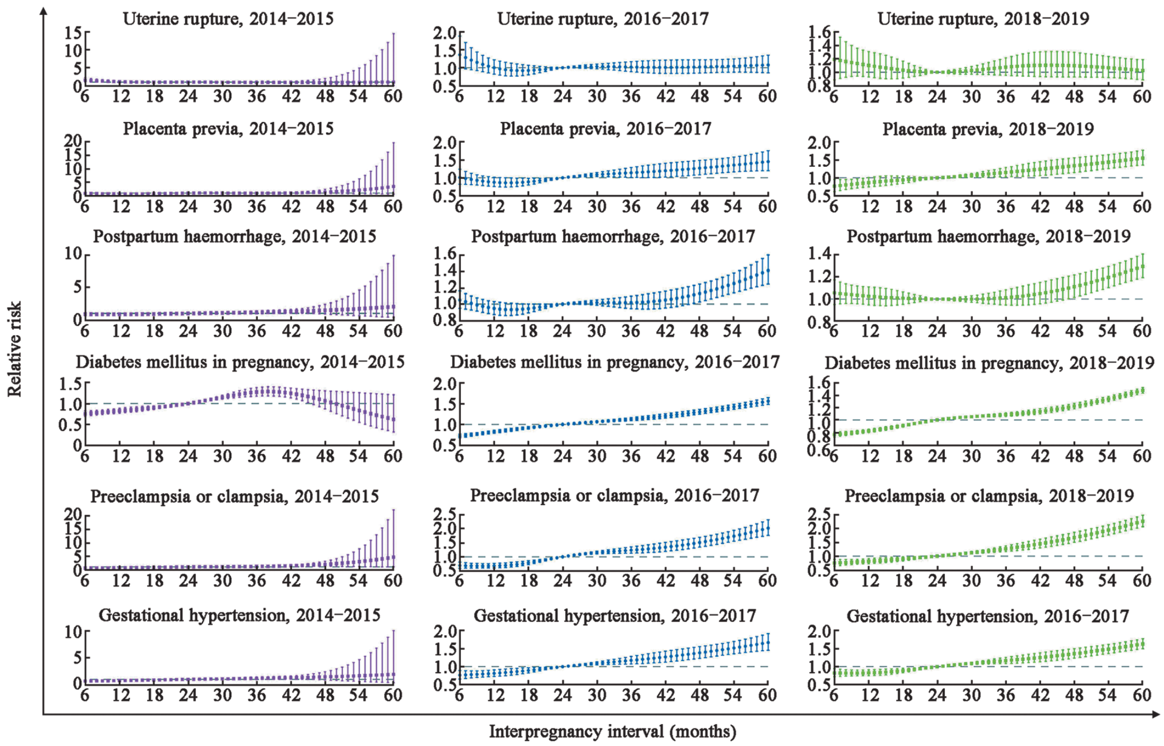

Figure 3: aRR of maternal outcomes according to IPI stratified by fertility policy period. Adjusted for: urban or rural areas, hospital level, inadequate prenatal examination, gestational age in previous pregnancy, maternal educational status, maternal age, delivery mode in previous pregnancy, parity, pregnant losses, and maternal complication. aRR: Adjusted relative risk; IPI: Interpregnancy interval.

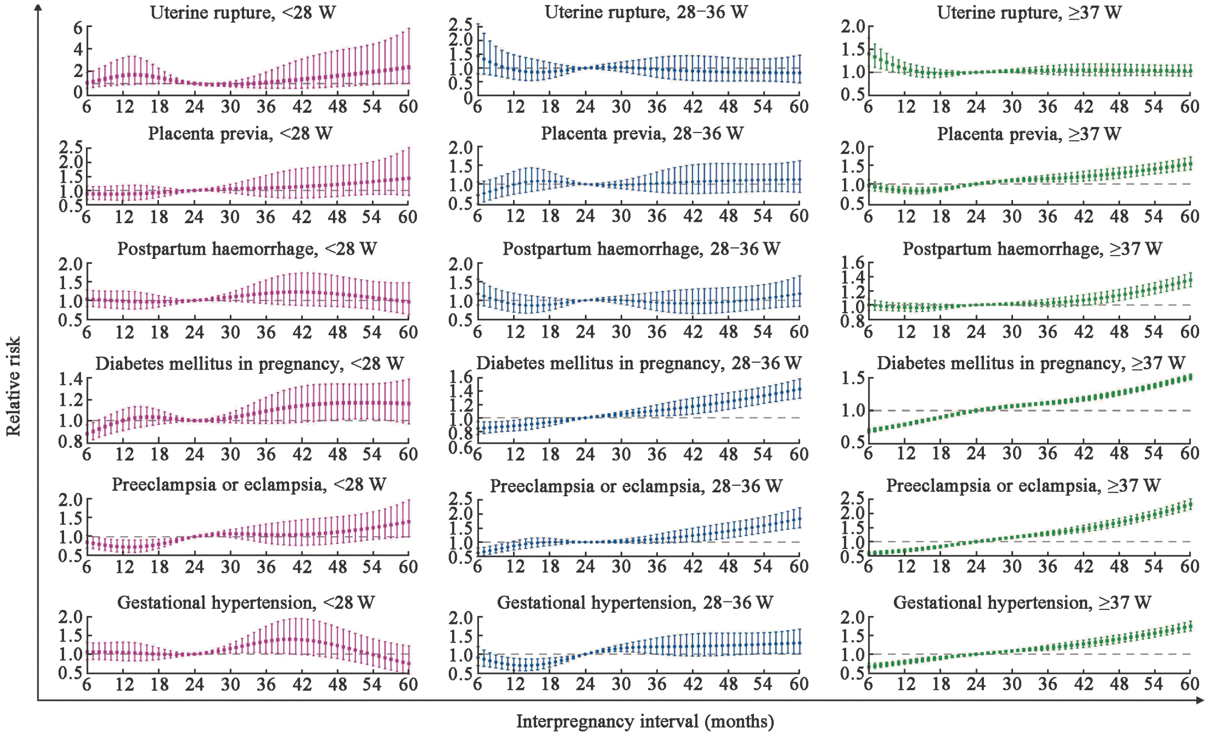

Figure 4: aRR of maternal outcomes according to IPI stratified by gestational age in previous pregnancy. Adjusted for: urban or rural areas, hospital level, inadequate prenatal examination, fertility policy period, maternal educational status, maternal age, delivery mode in previous pregnancy, parity, pregnant losses, and maternal complication. aRR: Adjusted relative risk; IPI: Interpregnancy interval.

Table 2: aRR of each outcome for pregnancies at 6-, 18-, 30-, 42-, and 60-month IPIs.

	IPIs, aRR (95% CI)*				
Outcomes	**6-month**	**18-month**	**36-month**	**48-month**	**60-month**
Preterm birth (VD)	1.63 (1.55, 1.71)	1.02 (0.99, 1.06)	0.99 (0.95, 1.03)	1.05 (0.99, 1.11)	1.18 (1.11, 1.26)
Preterm birth (CS)	1.10 (1.03, 1.19)	1.00 (0.96, 1.03)	1.04 (1.00, 1.08)	1.17 (1.11, 1.23)	1.39 (1.32, 1.47)
Low Apgar score	1.56 (1.36, 1.79)	1.00 (0.93, 1.09)	0.85 (0.77, 0.94)	0.82 (0.72, 0.93)	0.93 (0.81, 1.06)
LGA	0.77 (0.75, 0.79)	0.95 (0.94, 0.96)	1.05 (1.04, 1.07)	1.09 (1.07, 1.11)	1.13 (1.10, 1.15)
SGA	1.36 (1.32, 1.40)	1.05 (1.03, 1.07)	0.99 (0.96, 1.01)	0.99 (0.96, 1.02)	0.98 (0.94, 1.01)
Uterine rupture	1.31 (1.08, 1.59)	0.98 (0.91, 1.07)	1.04 (0.96, 1.13)	1.05 (0.94, 1.18)	1.04 (0.93, 1.17)
Placenta previa	0.91 (0.80, 1.03)	0.89 (0.83, 0.95)	1.13 (1.05, 1.21)	1.27 (1.15, 1.40)	1.50 (1.35, 1.67)
Postpartum hemorrhage	1.02 (0.95, 1.09)	0.96 (0.93, 1.00)	1.03 (0.98, 1.08)	1.13 (1.06, 1.21)	1.33 (1.24, 1.42)
Diabetes mellitus in pregnancy	0.74 (0.71, 0.76)	0.91 (0.89, 0.92)	1.11 (1.09, 1.14)	1.26 (1.23, 1.30)	1.50 (1.46, 1.54)
Preeclampsia or eclampsia	0.68 (0.62, 0.75)	0.84 (0.80, 0.89)	1.24 (1.17, 1.31)	1.58 (1.47, 1.70)	2.16 (2.02, 2.32)
Gestational hypertension	0.78 (0.71, 0.85)	0.89 (0.85, 0.93)	1.17 (1.11, 1.23)	1.37 (1.27, 1.47)	1.64 (1.53, 1.76)

*Adjusted for urban or rural areas, hospital level, inadequate prenatal examination, fertility policy period, gestational age in previous pregnancy, maternal educational status, maternal age, delivery mode in previous pregnancy, parity, pregnant losses, maternal complication, interactions of fertility policy period category, and previous pregnancy category. aRR: Adjusted relative risk; CI: Confidence interval; CS: Cesarean section; IPIs: Interpregnancy intervals; LGA: Large for gestational age; SGA: Small for gestational age; VD: Vaginal delivery.

In sensitivity analyses, the calculated E values indicated that confounding was unlikely to entirely explain the observed results [Supplementary Table 7, http://links.lww.com/CM9/B661].

Discussion

In the context of the rising proportion of second children and multiparas, there is an increasing need to recognize the association of IPIs and adverse maternal and neonatal outcomes. In our study, we found that approximately half of the women (51.86%) became pregnant again within an IPI of less than 24 months. A short IPI (≤6 months) was associated with an increased risk of preterm birth (VD), preterm birth (CS), a low Apgar score at 1 min, SGA, and uterine rupture, and a decreased risk of diabetes mellitus in pregnancy, preeclampsia or eclampsia, and gestational hypertension. A long IPI (≥60 months) was associated with an increased risk of preterm birth (VD), preterm birth (CS), LGA, placenta previa, postpartum hemorrhage, diabetes mellitus in pregnancy, preeclampsia or eclampsia, and gestational hypertension. The fertility policy change had an effect on the increase in IPIs but had little effect on the association of IPIs and adverse maternal and neonatal outcomes. The estimated risk of preterm birth (VD), preterm birth (CS), low Apgar scores, and SGA in women with short IPIs was higher among those with a previous term birth, while the decreased risk of diabetes mellitus in pregnancy was more profound among those who became pregnant again after a term birth. Rare notable differences were observed in the association between IPIs and other birth outcomes by infant gestational age in previous pregnancy.

Previous studies have also explored the association of IPIs and adverse maternal and neonatal outcomes in China. One of them was a multicenter retrospective study of 21 hospitals from 14 provinces.[15] The IPI distribution of that research was different from ours. In that study, over half of the women were pregnant within an IPI of 24–59 months. In our research, approximately half of the women were pregnant within an IPI less than 24 months. We found that all the participants in that study were from level 3 hospitals. Level 3 hospitals in China have advanced medical facilities and staff and specialize in difficult miscellaneous diseases and near misses. In our results, we included women from level 1 to level 3 hospitals, and we found that the more advanced the hospital was, the higher the proportion of women with a long IPI.

Previous research has explored the effect of IPIs on preterm birth, SGA, and LGA in South China from 2000 to 2015, before the implementation of the "universal two-child" policy.[4] Although adjusted with different covariates, the curves were consistent with our study. In our study, according to the comparison, we determined whether these associations were confounded by fertility policy changes. A significant IPI increment immediately after the announcement of the "universal two child" policy was found among primiparas. However, we found that the association of IPIs and adverse maternal and neonatal outcomes seemed rarely affected by the fertility policy. The curve of the association of IPIs and each adverse outcome was similar in different fertility phase periods.

In addition to fertility policy changes, we also wanted to explore the effect of infant gestational age in previous pregnancy. For neonatal outcomes in previous studies, we noticed that the estimated risk of preterm birth for women with short and long IPIs was higher among those with a previous term birth than a previous preterm birth.[3,21] The risk of preterm birth in women with short IPIs is consistent with the maternal depletion hypothesis.[8,40] Through further exploration in our study, we found that among women with previous term births, the risk of preterm birth (VD) was higher than that of preterm birth (CS) among those with short IPIs. However, in women with long IPIs, the risk of preterm birth (VD) was lower than that of preterm birth (CS). The delivery mode may be affected by various reasons, and research has shown that compared with VD, CS was associated with increased odds of maternal intensive care unit admission, maternal near misses, and neonatal intensive care unit admission.[41] In our research, although we could not separate iatrogenic preterm birth from spontaneous preterm birth, the associations between IPIs and preterm birth (VD) and IPIs and preterm birth (CS) were similar to those between IPIs and spontaneous preterm and iatrogenic preterm births.[42] As hypertension and placenta previa were confirmed as key factors in iatrogenic preterm births,[43] we interestingly found that the trend for preterm birth (CS) was consistent with that for placenta previa, preeclampsia or eclampsia, and gestational hypertension in women with long IPIs. For maternal outcomes, our results for all participants were consistent with another study of Chinese women, except the association of IPIs and preeclampsia.[14] In that research, a short IPI (<12 months) was associated with an increased risk of preeclampsia. However, two restrictions were observed in that study. First, the increased risk of preeclampsia in women with short IPIs may be contrary to the "physiological regression hypothesis" that during pregnancy, the maternal cardiovascular system and metabolic system gain growth-supporting capacities to support fetal growth. However, the increased blood volume and insulin level gradually decrease if the woman does not become pregnant again.[44,45] In our results, the risk of cardiovascular or metabolic system-related complications, such as diabetes mellitus in pregnancy, preeclampsia or eclampsia, and gestational hypertension, was generally decreased when the IPI was short. In addition, we found that the longer the previous gestational period was, the greater the decreased risk of these complications. Moreover, the results in that study were not adjusted for covariates such as preeclampsia in previous pregnancy, while research has demonstrated that women with prior preeclampsia have a higher risk of recurrence of preeclampsia.[46] And the degree of abnormal glucose metabolism in previous pregnancy was important in the recurrence of diabetes mellitus in pregnancy.[35] Our result was consistent with another meta-analysis that concluded that shorter intervals (less than 2 years) are not associated with an increased risk of recurrent preeclampsia, but longer intervals appear to increase the risk.[7] We further found that the estimated risk of preeclampsia or eclampsia, gestational hypertension, and diabetes mellitus in pregnancy for women with long IPIs increased more among women with a previous term birth than among those with a previous preterm birth or an infant with a gestational age less than 28 weeks. These differences need to be further explored.

There were some limitations of our research. First, cases enrolled in this study included women with at least two consecutive pregnancies documented in the national database who became pregnant again between 2014 and 2019. Thus, there was little chance for us to enroll women with long IPIs, especially IPIs above 60 months. Furthermore, there were still confounders, such as maternal economic status and fertility desire, that were not available in this research even though they are considered to have an effect on the association of IPIs and adverse maternal and neonatal outcomes.[47]

The association of IPIs and adverse outcomes may not be affected by factors such as fertility policy changes, while infant gestational age in previous pregnancy, especially a preceding term birth, may be a more important factor in the association of IPIs and adverse outcomes. In the future clinical practice of pregnancy health care, for pregnant women with shorter or longer IPIs, more targeted health care measures during pregnancy should be formulated according to their infant's gestational age in previous pregnancy.

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Conflicts of interest

None.

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