Optimized cutoff maternal age for adverse obstetrical outcomes: a multicenter retrospective cohort study in Urban China during 2011 to 2012

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Abstract

Background: China's two-child policy has led to a trend of aging in pregnancy which was associated with adverse outcomes. This study aimed to identify the clinically cutoff maternal age for adverse obstetric outcomes in China.

Methods: This secondary analysis of a multicenter retrospective cohort study included data of childbearing women from 39 hospitals collected in urban China during 2011 to 2012. Logistic regression was used to assess the adjusted odds ratios (aOR) of adverse outcomes in different age groups in comparison to women aged 20 to 24 years. The adjustments included the location of the hospital, educational level, and residence status. Clinically cutoff age was defined as the age above which the aOR continuously become both statistically ($P < 0.05$) and clinically (aOR > 2) significant.

Results: Overall, 108,059 women were recruited. In primiparae, clinically cutoff maternal ages for gestational diabetes (aOR: 2.136, 95% confidence interval [CI]: 1.856–2.458, $P < 0.001$), placenta previa (aOR: 2.400, 95% CI: 1.863–3.090, $P < 0.001$), cesarean section (aOR: 2.511, 95% CI: 2.341–2.694, $P < 0.001$), hypertensive disorder (aOR: 2.122, 95% CI: 1.753–2.569, $P < 0.001$), post-partum hemorrhage (aOR: 2.129, 95% CI: 1.334–3.397, $P < 0.001$), and low birth weight (aOR: 2.174, 95% CI: 1.615–2.927, $P < 0.001$) were 27, 31, 33, 37, 41, and 41 years, respectively. In multiparae, clinically cutoff ages for gestational diabetes (aOR: 2.977, 95%CI: 1.808–4.904, $P < 0.001$), hypertensive disorder (aOR: 2.555, 95% CI: 1.836–3.554, $P < 0.001$), cesarean section (aOR: 2.224, 95% CI: 1.952–2.534, $P < 0.001$), post-partum hemorrhage (aOR: 2.140, 95% CI: 1.472–3.110, $P < 0.001$), placenta previa (aOR: 2.272, 95% CI: 1.375–3.756, $P < 0.001$), macrosomia (aOR: 2.215, 95% CI: 1.552–3.161, $P < 0.001$), and neonatal asphyxia (aOR: 2.132, 95% CI: 1.461–3.110, $P < 0.001$) were 29, 31, 33, 35, 35, 41, and 41 years, respectively.

Conclusions: Early cutoff ages for gestational diabetes and cesarean section highlight a reasonable childbearing age in urban China. The various optimized cutoff ages for different adverse pregnancy outcomes should be carefully considered in childbearing women.

Keywords: Maternal age; Pregnancy outcomes; Clinical alarms; Parity

Introduction

Advanced maternal age is becoming a public health concern and is associated with higher risks of cesarean sections,[1-3] pregnancy complications, and adverse maternal-fetal outcomes.[1-7] An aging childbearing population is being observed worldwide.[7] The average maternal age of primiparae in the United States increased from 24.9 years in 2004 to 26.3 years in 2014.[8] In China, the age increased from 26.3 years in 2000 to 28.2 years in 2010. China's two-child policy in 2016 made 54 million women over the age of 35 years eligible for a second child. Multiparity and the number of mothers at an advanced age are expected to increase. Therefore, it would be a potential challenge for Chinese health policymakers and clinical practitioners to do the allocation of health resources and interventional strategies.[9,10]

There is no commonly accepted definition of advanced maternal age, although it was simply identified as women older than 35 years of age. Each adverse outcome had its own risk trend with maternal age.[11,12] Different threshold

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maternal ages (range, 25–41 years) were reported for different maternal and neonatal adverse health outcomes.[7] However, there has been no related investigation on pregnant women in China.

In this study, we speculated that there are various clinically cutoff maternal ages for different adverse pregnancy outcomes. We aimed to identify the optimal clinically cutoff maternal ages of each outcome for both primiparae and multiparae in urban China.

Methods

Ethical approval

The study was performed in accordance with the Chinese Ethical Standards of Human Experimentation and the *Declaration of Helsinki* 1975 (revised in 2000). Data of each patient was coded in an anonymous format and extracted from the medical records. Privacy protection was obtained. Institutional informed consent was also obtained from the Ethics Committee at each participating center (No. 2013–08). The need for personal informed consent was waived because we were unable to contact the participants due to the anonymous nature of the collected data.

Population

This was a secondary analysis of a multicenter retrospective study of the Chinese Obstetric Pregnancy and Delivery Collaborated Group. Methodological details are described elsewhere.[13] Briefly, data were collected regarding all births older than 24 gestational weeks between January 1, 2011 and December 31, 2012 at 39 centers in 14 Chinese cities (Beijing, Shanghai, Xi'an, Nanjing, Jinan, Chengdu, Shenyang, Wuhan, Guangzhou, Changchun, Urumqi, Hohhot, Taiyuan, and Cangzhou), which were all secondary or tertiary hospitals.

Inclusion and exclusion criteria

All women aged 20 to 50 years with a singleton pregnancy and birth at hospitals were included. Women with missing information on parity or maternal age were excluded.

Maternal age

Maternal age was defined as the age at delivery as extracted from the medical records and discharge summaries and was recorded as an integer.

Possible confounders

Possible confounders include parity, location of the hospital, educational level, and residence status, self-reported smoking and alcohol history, body mass index at first antenatal visit, history of diabetes mellitus, chronic hypertension, and abortion history.

Pre-specified subgroup analysis (nulliparous and multiparous) was performed to determine parity-specific clinically cutoff ages.

Regional heterogeneity (location of the hospital) is believed to be related to disease prevalence.[14] Educational level (bachelor's degree or above, vocational school or senior high school, and junior high school or below) is also known to affect pregnancy complications.[15] Residence status (local or migrant) has been reported to affect maternal mortality and cause severe morbidity.[16] Therefore, the formal analysis was adjusted for the location of the hospital, residence status, and educational level with pregnancy outcomes in our study, based on the findings from previous scientific literature, because all factors had a theoretical association with the outcomes.

History of self-reported smoking and alcohol consumption, diabetes mellitus, and maternal chronic hypertension may also affect the outcomes. These factors were not adjusted in the logistic analysis because of their low prevalence. We also did not adjust for abortion history and body mass index at first antenatal visit because these factors may only affect some outcomes [Table 1].

Outcomes

The following pregnancy outcomes were recorded: delivery method, pregnancy complications, and perinatal outcomes. Estimated due dates were established using the last menstrual dates and were confirmed by ultrasound in the first trimester.

The mode of delivery was divided into the vaginal and cesarean section. Cesarean section was not further classified as an elective or emergency.

Pregnancy complications included pre-term birth, placenta previa, placental abruption, placenta accreta, intra-hepatic cholestasis during pregnancy, anemia, gestational diabetes, hypertensive disorder, and post-partum hemorrhage.

Perinatal outcomes included low birth weight (birth weight <2500 g), macrosomia (birth weight >4000 g), neonatal asphyxia (1-min Apgar [appearance, pulse, grimace, activity, and respiration] score ≤ 7), chromosome abnormalities (based on karyotyping), structural anomalies (based on prenatal ultrasound and post-natal physical examination), stillbirth, and transfer to the neonatal intensive care unit (NICU).

Adverse pregnancy outcomes with the incidence of $\leq 1\%$ were excluded in further analyses; these outcomes included placental abruption, placenta accreta, penetrative placenta, implanted placenta, amniotic fluid embolism, pulmonary embolism, intra-hepatic cholestasis of pregnancy, structural abnormality, chromosome abnormality, and stillbirth.

Statistical analyses

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A two-tailed P-value <0.05 was defined as statistically significant. The Chi-squared test was used to analyze the association between obstetric outcomes and parity. Crude and adjusted logistic regression analyses were used to analyze the effects of maternal age on pregnancy outcomes.

Table 1: Maternal demographic characteristics in primiparae and multiparae.

Parameters	Primiparae ($n = 87,714$)	Multiparae ($n = 20,345$)
Maternal age (years)	27.64 ± 4.19	31.14 ± 5.09
Maternal residency		
Local	62,587 (71.353)	12,540 (61.637)
Nonlocal	25,091 (28.605)	7794 (38.309)
Missing	36 (0.041)	11 (0.054)
Maternal educational level		
Graduate or above	47,977 (54.697)	5966 (29.324)
Technical secondary school and high school	22,890 (26.096)	5989 (29.437)
Junior high school or below	13,962 (15.918)	7401 (36.377)
Missing	2885 (3.329)	989 (4.861)
Maternal self-reported smoking history		
Yes	181 (0.206)	91 (0.447)
No	87,533 (99.794)	20,254 (99.600)
Maternal self-reported drinking history		
Yes	805 (0.918)	164 (0.806)
No	86,909 (99.082)	20,181 (99.194)
Maternal BMI at first antenatal visit		
<19 kg/m^2	9474 (10.801)	1543 (7.584)
19–23 kg/m^2	29,577 (33.720)	6192 (30.435)
>23 kg/m^2	13,911 (15.859)	3154 (15.503)
Missing	34,752 (39.620)	9456 (46.478)
Maternal diabetes mellitus history		
Yes	57 (0.065)	17 (0.084)
No	87,657 (99.935)	20,328 (99.916)
Maternal chronic hypertension history		
Yes	90 (0.103)	65 (0.319)
No	87,624 (99.897)	20,280 (99.681)
Maternal abortion history		
No	56,894 (64.863)	9747 (47.909)
Yes	30,819 (35.136)	10,598 (52.091)
Missing	1 (0.001)	0

Data are presented as n (%) or mean ± standard deviation (SD). BMI: Body mass index.

Data were stratified according to the maternal age: the age group of 20 to 24 years was the reference. Data were divided into 2-year groups between 24 to 40 years of age and those no less than 41 years was identified as one group due to the small number of cases.

Logistic analysis was performed only for variables with incidence larger than 10 times the degrees of freedom. Data were stratified into primiparae and multiparae.

Statistically significant cutoff age was defined as the age at the first significant adjusted odds ratio (aOR) after which the aOR remained statistically significant ($P < 0.05$). Clinically cutoff age was defined as the first significant age after which the aOR remained no less than 2.[6]

Post-hoc subgroup analysis for maternal age and GDM stratified by the body mass index (BMI) at the first antenatal visit (18.5 kg/m^2 ≤ BMI < 24 kg/m^2 and BMI ≥ 24 kg/m^2), was performed in primiparae. We further assessed the interaction of BMI and maternal age as continuous variables. Interaction effects were calculated as relative excess risk interaction, synergy index, and attributable proportion.

Results

Data of 117,330 pregnant women were obtained; 9271 (7.9%) of them had missing data about parity or maternal age. Therefore, data of 108,059 (92.1%) pregnant women were used for analysis, which included 87,714 (81.2%) primiparae and 20,345 (18.8%) multiparae women.

Maternal demographic characteristics are summarized in Table 1. Compared to multiparous women, primiparous women were younger (31.14 ± 5.09 years *vs.* 27.64 ± 4.19 years), were more likely to be local residents (61.637% *vs.* 71.353%), and had a higher educational level (29.324% *vs.* 54.697%). Primiparous women had lower incidence of placenta previa (1.106% *vs.* 1.769%), anemia (5.627% *vs.* 8.548%), hypertensive disorder (4.869% *vs.* 6.424%), pre-term birth (6.436% *vs.* 9.717%), low birth weight (5.695% *vs.* 7.211%), macrosomia (5.125% *vs.* 6.311%), neonatal asphyxia (2.803% *vs.* 4.173%), and NICU admissions (2.297% *vs.* 3.775%) in comparison with multiparous women, but had higher rate of gestational diabetes (4.695% *vs.* 4.247%) and similar rate of post-partum hemorrhage (3.578% *vs.* 3.731%) [Table 2].

To assess the effects of maternal age on adverse pregnancy outcomes, the logistic analysis was performed. In the unadjusted logistic analysis, compared to maternity during 20 to 24 years, older maternal age increased the risks of cesarean section, the incidence of gestational diabetes mellitus, hypertensive disorder, pre-term birth, and post-partum hemorrhage, but decreased the risk of maternal anemia, in both primiparous and multiparous women. A positive linear rate of placenta previa was observed with age in primiparae, in contrast to the "J"-shaped trend in multiparae with the lowest point at 27 to 28 years [Figure 1].

In logistic analysis adjusted for demographic characteristics in primipara and multiparae, the respective significant threshold ages were 25 years and 25 years for cesarean section, 25 years and 25 years for placenta previa, 25 years and 27 years for gestational diabetes mellitus, 25 years and 37 years for placenta accrete spectrum, 31 years and 27 years for gestational hypertension disorders, and 25 years and 35 years for post-partum hemorrhage. The respective clinically cutoff ages in primiparae *vs.* multiparae ranged from 27 years to 41 years for cesarean section (33 years *vs.* 33 years), placenta previa (31 years *vs.* 35 years), placenta accrete spectrum (31 years *vs.* 39 years), gestational diabetes mellitus (27 years *vs.* 29 years), hypertensive disorder (37 years *vs.* 31 years), post-partum hemorrhage (41 years *vs.* 35 years), low birth weight (41 years *vs.* none), macrosomia (none *vs.* 41 years), and neonatal asphyxia (none *vs.* 41 years) [Figure 2, Tables 3 and 4].

Table 2: Adverse maternal and neonatal outcomes in primiparae and multiparae.

Parameters	Primiparae ($n = 87,714$)	Multiparae ($n = 20,345$)
Adverse maternal health outcomes		
Delivery mode		
Eutocia	38,399 (43.778)	9835 (48.341)
CS	48,093 (54.829)	10,414 (51.187)
Forceps	1216 (1.386)	96 (0.472)
Missing	6 (0.007)	0
Placenta previa	970 (1.106)	360 (1.769)
Missing	33 (0.038)	8 (0.039)
Placenta abruption	422 (0.481)	157 (0.772)
Missing	5 (0.006)	2 (0.010)
Placenta accrete spectrum disorders	916 (1.044)	300 (1.475)
Missing	7 (0.008)	2 (0.010)
PPH	3138 (3.578)	759 (3.731)
Missing	0	0
AFE	39 (0.044)	21 (0.103)
Missing	3 (0.003)	1 (0.005)
Pulmonary embolism	2 (0.002)	2 (0.010)
Missing	1 (0.001)	0
ICP	950 (1.083)	195 (0.958)
Missing	0	0
Anemia	4936 (5.627)	1739 (8.548)
Missing	11 (0.013)	3 (0.015)
Hypertensive disorder	4271 (4.869)	1307 (6.424)
Missing	0	0
Gestational diabetes	4118 (4.695)	864 (4.247)
Missing	133 (0.152)	34 (0.167)
Adverse perinatal outcomes		
Pre-term birth	5645 (6.436)	1977 (9.717)
Missing	0	0
Low birth weight	4995 (5.695)	1467 (7.211)
Missing	1368 (1.560)	422 (2.074)
Macrosomia	4495 (5.125)	1284 (6.311)
Missing	1368 (1.560)	422 (2.074)
Neonatal asphyxia	2459 (2.803)	849 (4.173)
Missing	2923 (3.332)	365 (1.794)
Still birth	133 (0.152)	41 (0.202)
Missing	164 (0.187)	75 (0.369)
NICU	2015 (2.297)	768 (3.775)
Missing	297 (0.339)	116 (0.570)

Data are presented as *n* (%). CS: Cesarean section; PPH: Post-partum hemorrhage; AFE: Amniotic fluid embolism; ICP: Intra-hepatic cholestasis of pregnancy; NICU: Neonatal intensive care unit.

Our post-hoc subgroup analysis revealed a similar trend of GDM with maternal age in the normal BMI group and the overweight group. Maternal BMI appeared to exhibit a synergistic additive interaction with maternal age in terms of GDM prevalence [Figure 3]. A small interaction was observed between maternal age and BMI. The relative excess risk interaction, synergy index, and attributable proportion due to interaction were 0.051 (95% confidence interval [CI]: 0.016–0.104), 0.033 (95% CI: 0.012–0.059), and 1.108 (95% CI: 1.052–1.160), respectively.

Discussion

In this large multicenter cohort study, statistically significant and clinically meaningful cutoff maternal ages were optimized for specific adverse pregnancy outcomes in primiparous and multiparous women in urban China. The clinically meaningful cutoff ages were less than 35 years for gestational diabetes and cesarean section in both nulliparous and multiparous women, for placenta previa and placenta accreta in nulliparous women, and for hypertensive disorder in multiparous women. It was suggested that a targeted intervention strategy should be adopted before the maternal age of 35 years to avoid these outcomes. On the contrary, the effects of maternal aging on most neonatal outcomes were not clinically significant until 41 years of age.

In this study, both statistical significance and clinically meaningful cutoff ages were assessed as risk factors for each adverse outcome. In some cases, the difference was too small to be clinically alarming, however, statistical significance was still observed for such outcomes due to the large sample size that was powerful enough to detect small changes in the risk between the age groups. In a previous report, the increased risk was not considered large enough and the authors recommended that it should be interpreted cautiously if *P* was less than 0.05 and aOR was not larger than 2.0.[6] In clinical practice, however, the actual magnitude of the difference is more important than the statistical significance. In our study, the risks increased by two-fold for gestational diabetes at the age of 27 years in nulliparous and 29 years in multiparous women, and similar changes for cesarean section were noted at 33 years of age. Therefore, the strategy of prevention and treatment against the influence of maternal age on certain outcomes should be considered in women aged less than 35 years, and even at 30 years, irrespective of the public health policy or clinical practice.

The trends of pregnancy outcomes in this study were similar to those reported in other studies, most of which demonstrated a continuous linear association of outcomes with maternal age.[1,2,6] Only the association with pre-term labor, asphyxia, and NICU admission demonstrated a J-shaped trend. Statistical cutoff ages for each obstetric outcome ranged from 25 to 41 years and varied for each outcome. In previous studies, advanced maternal age was defined as that not less than 35 years based on decreased fertility, increased miscarriage, chromosomal abnormalities, hypertensive disorder, and stillbirth in women in this group.[17] However, recent reports have indicated that the effect of maternal age on adverse pregnancy outcomes seems to be continuous and linear and could exist before the maternal age of 35 years and vary for different outcomes.[2] The risk of fetal death was reported to be higher in women aged 30 to 34 years than in women aged 25 to 29 years,[18] and the risk of pre-term birth has been reported to increase since the age of 30 years.[19] Klemetti *et al*[7] found that the statistical threshold age for each adverse outcome – including maternity care and maternal and neonatal health outcomes – ranged from 25 to 38 years in nulliparous women, with women aged 20 to 24 years serving as the reference.

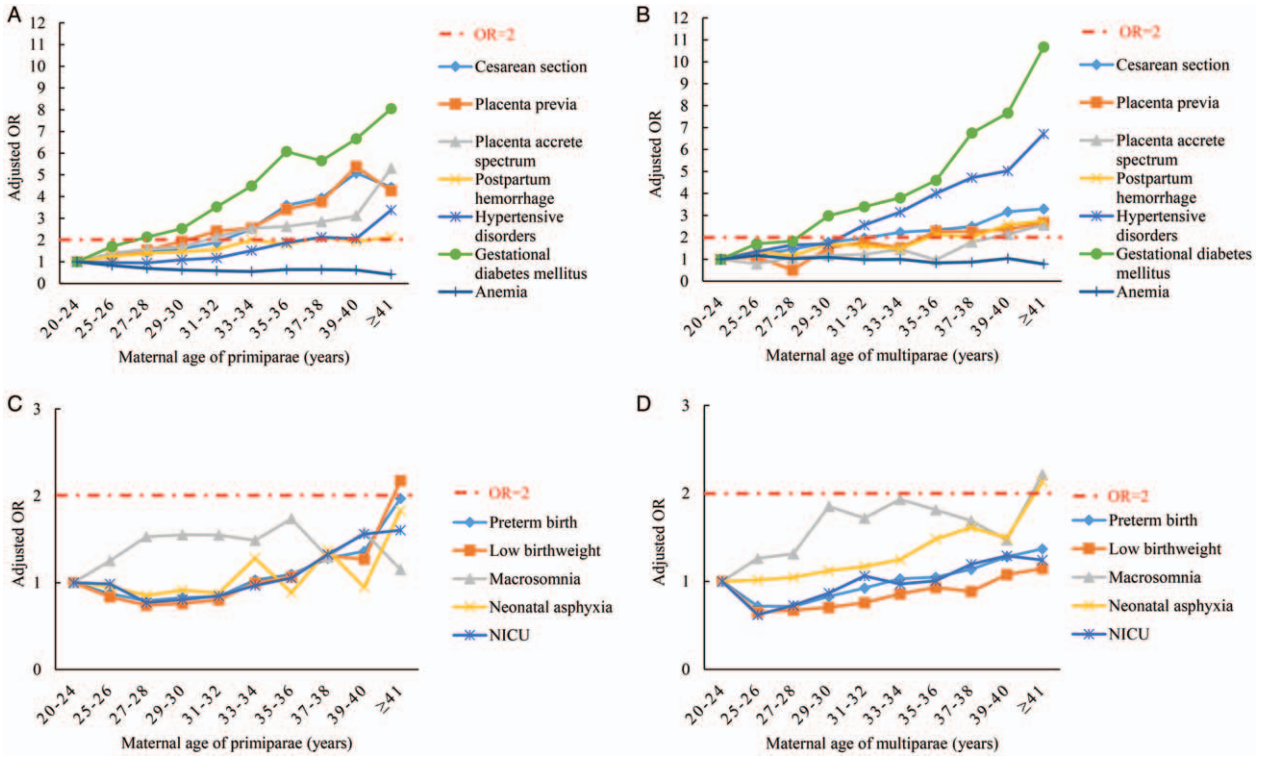

Figure 1: OR of adverse outcomes in primiparae and multiparae adjusted for location of the hospital, educational level, and residence status. (A) Maternal outcomes in primiparae. (B) Maternal outcomes in multiparae. (C) Neonatal outcomes in primiparae. (D) Neonatal outcomes in multiparae. OR: Odds ratio.

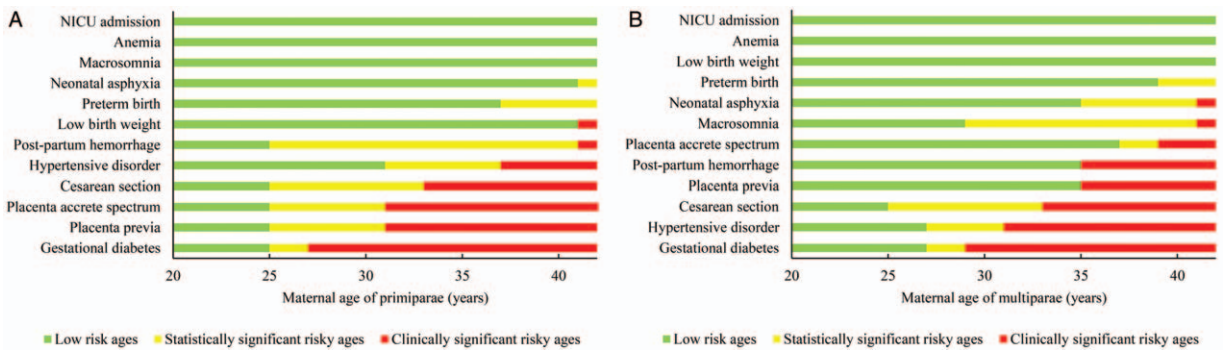

Figure 2: Statistically significant ages (aOR > 1 and $P < 0.05$) and clinically significant ages (aOR > 2 and $P < 0.05$) of adverse pregnancy outcomes in (A) primiparae and (B) multiparae, compared with 20 to 24 years. NICU: Neonatal intensive care unit; aOR: Odds ratio adjusted for location of the hospital, educational level, and residence status; CI: Confidence interval.

We found that the risk of cesarean section was linearly related to maternal age and was clinically significant at 33 years in both nulliparous and multiparous women. However, the threshold age for cesarean section was reported as 25 years in nulliparous women in a study from Finland.[7] Most studies have reported that the cesarean section rate significantly increased in women aged 35 or 40 years.[1,3,20,21] Song *et al*[22] reported that the risk of cesarean delivery increased 7.4-fold in women aged more than 35 years, as compared with women aged less than 25 years in Beijing.

In our study, the risk of gestational diabetes was linearly associated with maternal age and significantly increased beyond the cutoff age of 25 years, which is similar to that previously reported in nulliparous women.[7] Lao *et al*[23] reported that the risk in women aged 25 to 29 years increased 2.59 times compared to that in women aged 20 to 24 years. Our results also demonstrated two-fold increased risk in nulliparous and multiparous women at cutoff ages of 27 and 29 years, respectively. As the average childbearing maternal age is 28.2 years in China, the cutoff age of 30 years should be considered in clinical practice for stronger prevention, screening, and intervention strategies.

Our study demonstrated that the statistical and clinical cutoff ages for hypertensive disorder in pregnancy were younger in multiparous women (27 and 31 years, respectively) than in nulliparous women (31 and 37 years, respectively). Most previous studies had focused on

Table 3: Adjusted* odds ratio (95% confidence interval) of maternal and fetal health outcomes according to maternal age in primiparae.

		Maternal age (years)									
Parameters		**20–24**	**25–26**	**27–28**	**29–30**	**31–32**	**33–34**	**35–36**	**37–38**	**39–40**	**≥41**
Maternal health outcomes											
Cesarean section	Control	1.337 (1.276, 1.400)	1.431 (1.368, 1.496)	1.606 (1.533, 1.683)	1.881 (1.780, 1.987)	2.511 (2.341, 2.694)	3.600 (3.278, 3.954)	3.924 (3.475, 4.431)	5.081 (4.248, 6.077)	4.428 (3.468, 5.654)	
Placenta previa	Control	1.323 (1.024, 1.711)	1.525 (1.201, 1.936)	1.935 (1.532, 2.443)	2.400 (1.863, 3.090)	2.551 (1.911, 3.404)	3.416 (2.499, 4.669)	3.767 (2.612, 5.432)	5.376 (3.515, 8.224)	4.270 (2.278, 8.004)	
Placenta accrete spectrum	Control	1.389 (1.074, 1.796)	1.576 (1.242, 2.000)	1.678 (1.320, 2.134)	2.143 (1.652, 2.780)	2.537 (1.903, 3.382)	2.621 (1.873, 3.667)	2.831 (1.896, 4.229)	3.120 (1.835, 5.305)	5.297 (2.939, 9.548)	
Post-partum hemorrhage	Control	1.247 (1.084, 1.434)	1.389 (1.220, 1.581)	1.457 (1.277, 1.662)	1.555 (1.342, 1.801)	2.00 6 (1.703, 2.363)	1.801 (1.468, 2.210)	2.113 (1.664, 2.683)	1.936 (1.377, 2.723)	2.129 (1.334, 3.397)	
Hypertensive disorder	Control	0.958 (0.856, 1.072)	0.945 (0.848, 1.054)	1.087 (0.975, 1.212)	1.170 (1.034, 1.325)	1.514 (1.315, 1.743)	1.878 (1.596, 2.209)	2.122 (1.753, 2.569)	2.063 (1.590, 2.677)	3.378 (2.499, 4.565)	
Gestational diabetes	Control	1.701 (1.457, 1.986)	2.136 (1.856, 2.458)	2.518 (2.190, 2.895)	3.521 (3.046, 4.071)	4.490 (3.839, 5.251)	6.074 (5.123, 7.202)	5.651 (4.616, 6.918)	6.655 (5.173, 8.562)	8.042 (5.829, 11.096)	
Anemia	Control	0.828 (0.754, 0.910)	0.689 (0.627, 0.758)	0.619 (0.560, 0.685)	0.580 (0.513, 0.655)	0.549 (0.468, 0.644)	0.634 (0.523, 0.768)	0.638 (0.500, 0.814)	0.618 (0.439, 0.870)	0.412 (0.231, 0.737)	
Neonatal health outcomes											
Pre-term birth	Control	0.872 (0.795, 0.956)	0.792 (0.724, 0.867)	0.827 (0.753, 0.907)	0.840 (0.752, 0.937)	1.032 (0.908, 1.172)	1.096 (0.938, 1.280)	1.279 (1.064, 1.536)	1.363 (1.067, 1.742)	1.969 (1.469, 2.641)	
Low birth weight	Control	0.836 (0.760, 0.920)	0.741 (0.673, 0.815)	0.761 (0.689, 0.840)	0.801 (0.712, 0.900)	0.997 (0.870, 1.143)	1.067 (0.904, 1.261)	1.307 (1.078, 1.585)	1.271 (0.978, 1.652)	2.174 (1.615, 2.927)	
Macrosomia	Control	1.251 (1.118, 1.400)	1.530 (1.379, 1.697)	1.550 (1.393, 1.725)	1.549 (1.371, 1.749)	1.486 (1.280, 1.724)	1.736 (1.456, 2.070)	1.292 (1.013, 1.649)	1.582 (1.165, 2.148)	1.150 (0.702, 1.883)	
Neonatal asphyxia	Control	0.954 (0.839, 1.086)	0.852 (0.746, 0.973)	0.915 (0.797, 1.050)	0.880 (0.743, 1.042)	1.281 (1.066, 1.540)	0.887 (0.683, 1.151)	1.371 (1.045, 1.798)	0.949 (0.619, 1.453)	1.831 (1.183, 2.834)	
Transferring to NICU	Control	0.986 (0.856, 1.136)	0.771 (0.666, 0.893)	0.805 (0.692, 0.937)	0.847 (0.706, 1.017)	0.966 (0.775, 1.204)	1.054 (0.807, 1.378)	1.326 (0.972, 1.808)	1.560 (1.062, 2.291)	1.604 (0.966, 2.664)	

*Adjusted for the location of the hospital, educational level, and residence status. NICU: Neonatal intensive care unit.

Table 4: Adjusted* odds ratio (95% confidence interval) of maternal and fetal health outcomes according to maternal age in multiparae.

		Maternal age (years)									
Parameters		**20–24**	**25–26**	**27–28**	**29–30**	**31–32**	**33–34**	**35–36**	**37–38**	**39–40**	**≥41**
Maternal health outcomes											
Cesarean section	Control	1.213 (1.060, 1.389)	1.445 (1.272, 1.642)	1.778 (1.571, 2.011)	1.964 (1.733, 2.225)	2.224 (1.952, 2.534)	2.333 (2.040, 2.668)	2.497 (2.161, 2.886)	3.161 (2.665, 3.751)	3.295 (2.730, 3.977)	
Placenta previa	Control	1.104 (0.611, 1.994)	0.511 (0.260, 1.005)	1.526 (0.916, 2.542)	1.784 (1.078, 2.953)	1.524 (0.900, 2.580)	2.272 (1.375, 3.756)	2.253 (1.335, 3.802)	2.360 (1.332, 4.180)	2.673 (1.492, 4.792)	
Placenta accrete spectrum	Control	0.785 (0.403, 1.528)	1.073 (0.608, 1.895)	1.181 (0.689, 2.024)	1.216 (0.709, 2.085)	1.452 (0.853, 2.474)	0.974 (0.545, 1.738)	1.792 (1.038, 3.093)	2.135 (1.187, 3.838)	2.569 (1.418, 4.654)	
Post-partum hemorrhage	Control	1.364 (0.897, 2.075)	1.154 (0.767, 1.735)	1.684 (1.161, 2.443)	1.622 (1.112, 2.364)	1.472 (0.996, 2.177)	2.140 (1.472, 3.110)	2.004 (1.350, 2.975)	2.576 (1.695, 3.916)	2.740 (1.770, 4.241)	
Hypertensive disorder	Control	1.347 (0.924, 1.963)	1.648 (1.159, 2.342)	1.700 (1.208, 2.392)	2.555 (1.836, 3.554)	3.146 (2.257, 4.386)	4.004 (2.885, 5.558)	4.716 (3.381, 6.576)	5.024 (3.526, 7.157)	6.712 (4.696, 9.594)	
Gestational diabetes	Control	1.704 (0.954, 3.044)	1.826 (1.064, 3.133)	2.977 (1.808, 4.904)	3.398 (2.068, 5.583)	3.795 (2.310, 6.237)	4.599 (2.805, 7.541)	6.758 (4.129, 11.059)	7.663 (4.601, 12.762)	10.675 (6.401, 17.804)	
Anemia	Control	1.171 (0.933, 1.470)	1.023 (0.821, 1.275)	1.092 (0.883, 1.350)	0.984 (0.792, 1.222)	0.996 (0.791, 1.253)	0.833 (0.652, 1.064)	0.867 (0.666, 1.130)	1.033 (0.769, 1.387)	0.783 (0.553, 1.111)	
Neonatal health outcomes											
Pre-term birth	Control	0.718 (0.567, 0.909)	0.715 (0.574, 0.892)	0.829 (0.675, 1.019)	0.925 (0.753, 1.136)	1.029 (0.835, 1.269)	1.047 (0.847, 1.295)	1.138 (0.913, 1.418)	1.280 (1.001, 1.638)	1.369 (1.054, 1.778)	
Low birth weight	Control	0.646 (0.499, 0.837)	0.671 (0.529, 0.853)	0.705 (0.561, 0.885)	0.758 (0.603, 0.952)	0.857 (0.678, 1.082)	0.931 (0.737, 1.176)	0.885 (0.689, 1.137)	1.077 (0.816, 1.422)	1.145 (0.851, 1.540)	
Macrosomia	Control	1.262 (0.921, 1.728)	1.314 (0.975, 1.770)	1.851 (1.402, 2.442)	1.719 (1.296, 2.280)	1.931 (1.450, 2.572)	1.813 (1.351, 2.434)	1.689 (1.235, 2.311)	1.472 (1.026, 2.112)	2.215 (1.552, 3.161)	
Neonatal asphyxia	Control	1.015 (0.711, 1.447)	1.046 (0.748, 1.461)	1.120 (0.813, 1.544)	1.169 (0.847, 1.613)	1.246 (0.895, 1.734)	1.480 (1.069, 2.051)	1.613 (1.153, 2.256)	1.494 (1.016, 2.196)	2.132 (1.461, 3.110)	
Transferring to NICU	Control	0.620 (0.426, 0.902)	0.727 (0.518, 1.020)	0.867 (0.634, 1.186)	1.062 (0.781, 1.445)	0.970 (0.702, 1.341)	1.007 (0.726, 1.396)	1.194 (0.857, 1.663)	1.290 (0.886, 1.876)	1.243 (0.834, 1.852)	

*Adjusted for the location of the hospital, educational level, and residence status. NICU: Neonatal intensive care unit.

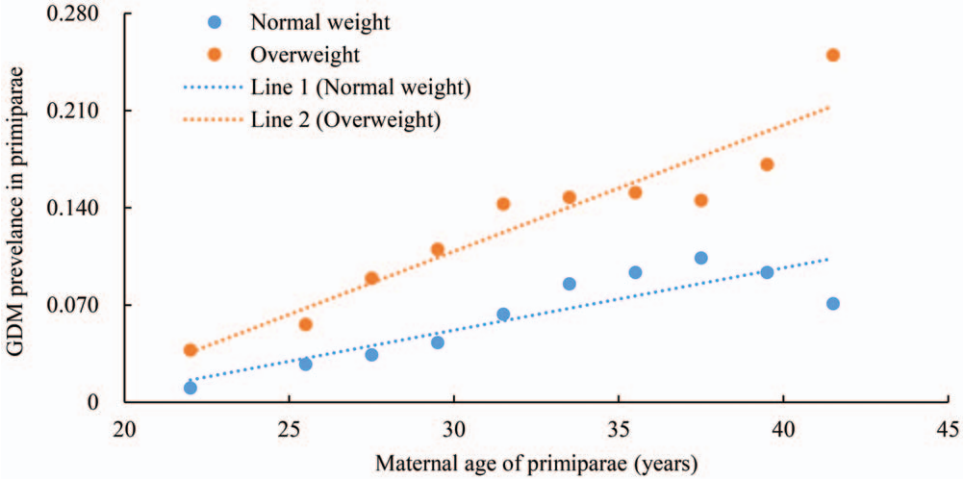

Figure 3: Prevalence of GDM raises at different speed ($P_0 = 0.005$) with maternal age in normal weight (18.5 kg/m^2 ≤ BMI < 24.0 kg/m^2, Line 1, $R_1^2 = 0.7704$, $P_1 = 0.0008$) and overweight (BMI ≥ 24 kg/m^2, Line 2, $R_2^2 = 0.8914$, $P_2 < 0.0001$) primiparae. GDM: Gestational diabetes mellitus; BMI: Body mass index.

nulliparous women to investigate the influence of maternal age on hypertensive disorders[6,12]; however, only few have focused on the effects of parity. Ngowa *et al*[24] reported that the risk of pre-eclampsia increased by 2.4 times in multiparous women older than 40 years as compared to that in women aged 20 to 29 years, with similar risks in nulliparous women. This disparity may be attributable to the variations in the etiology of hypertension disorders between nulliparous and multiparous women. Alterations in maternal immune adaption are generally believed to cause pregnancy complications like pre-eclampsia because maternal immunity has to adapt and tolerate the invasion of allogeneic feto-placental tissue during the first pregnancy and less so in subsequent pregnancies.[25] Pre-eclampsia in nulliparous women was more likely to be associated with disruption of the maternal immune adaption than that in multiparous women.

This study has some limitations. First, some potential confounders, such as body weight index, medical history, use of assisted conception, and smoking history, were not adjusted because of limited data. Second, pregnancy complications or adverse pregnancy outcomes with low incidence (<1%) were not included in the final analysis. Third, women aged no less than 41 years were categorized into one group because of the small number of participants; further studies are needed to more accurately identify the threshold ages in women over 41 years. Fourth, our data from different centers may have some internal heterogeneity in diagnostic criteria, which may have resulted in some bias. However, the diagnoses at each center were mostly based on the temporary domestic diagnostic criteria and the data extraction was performed by trained doctors to reduce the bias. We adjusted for the location of the hospital to eliminate the effects of center bias on our results.

Furthermore, the age at delivery was used instead of the age at fertilization as the maternal age in the study because of the limitations of the data source. However, this does not affect our conclusions due to the following reasons. First, most of the outcomes studied occur in the third trimester, close to the age at delivery. Second, the age at delivery was the same as, or 1 year older than, the age at fertilization when recorded as an integer. Moreover, 2-year age groups were employed in this study. Therefore, the difference in the definition of maternal age may only lead to a slightly older clinically cutoff age than what has been reported here; therefore, our finding that the risk of some adverse outcomes may reach clinical significance before 35 years of age remains valid.

In conclusion, optimized cutoff ages should be determined individually for different pregnancy complications and adverse neonatal outcomes. Our study suggests early cutoff childbearing ages for GDM (27 years in nulliparous and 29 years in multiparous women) and cesarean section (33 years in both nulliparous and multiparous women), that would warrant further clinical interventions, policies, resource allocation, and social security to prevent major adverse outcomes.

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Conflicts of interest

None.

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