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Optimal Timing for Elective Cesarean Delivery in a Chinese Population

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Objective: To assess the relationship between the timing of elective cesarean delivery on maternal request (CDMR) at term and perinatal outcomes in a Chinese population.

Methods: We conducted a retrospective cohort study of mode of delivery at a large obstetric center in Shanghai China between 2007-2014. Eligibility criteria included: term nulliparous women with a singleton gestation undergoing CDMR.

Results: There were 19,939 women delivered by CDMR without indications, with 5.9% performed at 37-37 6/7 weeks, 36.2% at 38-38 6/7 weeks, 38.4% at 39-39 6/7 weeks, 15.4% at 40-40 6/7 weeks, 4.0% at ⩾41 weeks. As compared with births at 39-39 6/7 weeks, births at 37 weeks were associated with an increased odds of neonatal respiratory disease (aOR: 4.82; 95% CI:3.35-6.94), neonatal infection (aOR: 3.68; 95% CI:1.80-7.52), hypoglycemia (aOR:3.85; 95%CI:2.29-6.48), hyperbilirubinemia (aOR:3.50; 95%CI:2.12-5.68), neonatal intensive care admission (aOR: 3.73; 95% CI:2.84-4.89) and prolonged hospitalization (aOR:7.51; 95% CI:5.10-11.07). Births at 38 weeks, 40 weeks, or ⩾41 weeks were also associated with an increased odds of neonatal respiratory disease with corresponding aORs (95% CI) of 2.26(1.71-3.00), 1.97(1.33-2.94) and 2.91(1.80-4.70) respectively.

Conclusion: CDMR performed at 39-39 6/7 complete weeks was associated with better neonatal outcomes than earlier or later delivery in a Chinese population.

Strengths and limitations

- It is a large hospital-based retrospective cohort study, with data abstracted from electronic medical records.
- We performed a detailed examination of each woman's record such that the indication for cesarean could be clearly ascertained. IPMCHH's policy requiring a consent form for CDMR made us able to determine truly non-medically indicated pre-labor cesarean deliveries.
- The study population had a low body mass index and was very homogeneous (99% Han) which strengthened our findings but may limit its applicability to other populations.
- There were only five neonatal deaths and one intrapartum stillbirth despite the large population studied.

Introduction

Infants born before 39 weeks of gestation are believed to be at increased risk for neonatal adverse respiratory outcomes and a composite adverse neonatal outcome. The risk increases progressively as gestational age at birth declines, especially when the infants are delivered by antepartum cesarean section without labor [1-4]. As a result, national clinical practice guidelines in the UK, the USA, and Canada recommend that planned caesareans should not be performed prior to 39 weeks of gestation without specific indications [5-7]. However, the differences in neonatal outcomes based on gestational age have been reported varies in different race and shorter gestational length has been

observed in certain ethnic groups. Some studies suggested that the advantages of waiting until 39 weeks to perform planned cesarean delivery for white women may not be evident in South Asians [8-9]. Without the direct evidence from a Chinese population study, the guideline of waiting to 39 weeks has not been formally implemented in China. The data concerning timing of elective cesarean section has largely come from women undergoing repeat procedures [1,4]. Only few studies have included small proportion of primary procedures [2,3].

China has the highest cesarean delivery (CD) rate in the world. A major reason for the high CD rate is the large proportion of non-indicated cesarean delivery on maternal request (CDMR)[10-13]. CDMR has actually become the most common reason for CD in most developed areas of China. Many factors, including the parents' preference of a specific day such as a birth day and physician convenience, have contributed to CD before 39 gestational weeks [10]. There is also increasing enthusiasm for CDMR in the western countries [14]. The timing of primary elective cesarean delivery has increasingly important public health implications. Therefore, we undertook the present study of a large, retrospective cohort of women to assess the relationship between gestational age at delivery and the risk of adverse perinatal outcomes in a Chinese nulliparous population.

MATERIALS AND METHODS

Study Design

We examined data from all pregnant women receiving care at the International Peace Maternity & Child Healthcare Hospital (IPMCHH), Shanghai Jiaotong University from January 1, 2007 through December 31, 2014. IPMCHH is one of the largest obstetric care centers in Shanghai, with 11,000~ 17,000 annual deliveries with over 90% women being nulliparous due to the Chinese one-child policy which ended in 2015. The study was approved by the ethics review board at IPMCHH.

Study Population

Eligibility criteria for the current study included: nulliparous women with singletons who delivered at term. Those with major fetal anomalies were excluded.

Data Collection

The IPMCHH research group and information engineer extracted and abstracted data from the hospital electronic medical record according to criteria set forth on the standardized data collection form. Types of information that were abstracted include: maternal demographic characteristics, medical history, reproductive and prenatal history, labor and delivery summaries and postpartum and neonatal information. The data were then de-identified prior to analysis.

CDMR was defined as an antepartum cesarean section performed on maternal request without medical indications which has been described previously [10]. Cases of CDMR could be identified in this study as IPMCHH

requires that a signed patient consent form outlining the risks and benefits of CD be retained in the medical record. The timing of delivery was determined in completed weeks of gestation such that 37 weeks (for example) included deliveries at 37 0/7–37 6/7 weeks. Gestational age was based on the combination of last menstrual period and first-trimester ultrasound.

The stillbirth rates per 1,000 ongoing pregnancies were calculated in the whole cohort of 81,507eligible women. The following neonatal outcomes calculated in the CDMR group were studied: neonatal mortality at less than 28 days, respiratory complications (registered as respiratory distress syndrome(RDS), transient tachypnea of the newborn, pneumothorax), hypoglycemia, necrotizing enterocolitis, hypoxic–ischemic encephalopathy, meconium aspiration syndrome, neonatal infection, hyperbilirubinemia, admission to the neonatal intensive care unit(NICU), and prolonged hospitalization (5 days or longer). The diagnosis of RDS required signs of respiratory distress, consistent radiologic features, and oxygen therapy with a fraction of inspired oxygen (FiO2) of 0.40 or greater for at least 24 hours or until death. Transient tachypnea of the newborn was defined by the presence of tachypnea within hours after birth and typical radiologic findings. The diagnosis of hypoglycemia required a serum or plasma glucose level of less than 2.5 mmol/l or treatment with intravenous glucose. Neonatal infection included pneumonia, sepsis, meningitis or antibiotic management for 3 days or more.

Data were analyzed with the use of SAS software, version 9.2 (SAS Institute, Cary NC). Descriptive statistics included means and standard deviations for continuous variables, and numbers and percentages for categorical variables. The incidence of adverse maternal and neonatal outcomes was calculated for each completed week of gestation at the time of CD. The Cochran–Armitage test for trend was used to assess trends in the incidence rates of outcomes. Adjusted odds ratios for the association between neonatal outcomes and gestational age at delivery relative to 39 completed weeks of gestation were derived from logistic-regression models that included maternal age, pre-pregnancy body-mass index, education, insurance status, type of conception, maternal chronic medical conditions, and pregnancy complications. A nominal two-sided P value of less than 0.05 was considered statistically significant.

Results

We abstracted data from 98,892 pregnancies to 95,603 unique women that received care at IPMCHH from 2007-2014. After restricting the sample to nulliparous women with singletons who delivered at term, we were left with 81,507 (82.4%) pregnancies to the same number of women for analysis. There were 48 stillbirths after 37^{+0} gestational weeks in this cohort. At 37, 38, 39, 40, 41 gestational weeks, the stillbirth rates per 1,000 ongoing pregnancies were 0.20, 0.20, 0.26, 0.07 and 0.16, respectively (P for GW trend <0.05) (Table 1). In the other 81,459 women with a live fetus, there were 50,912 women who

attempted vaginal delivery (spontaneous vaginal birth, assisted vaginal delivery, or intrapartum CD), 10,608 antepartum CD with indications. We identified 19,939 women delivered by CDMR (Fig. 1). Among the women who underwent elective CDMR at term, 5.9% underwent the procedure at 37-37 6/7 weeks, 36.2% at 38-38 6/7 weeks, 38.4% at 39-39 6/7 weeks, 15.4% at 40-40 6/7 weeks and 4.0% at ⩾41 weeks. Thus, 42.1% CDMR were performed before 39 weeks of gestation.

More than 99% of the women in our study population were of Han ethnicity. Baseline and obstetric characteristics of the study population are shown in Table 1. Gestational age was confirmed by a first- trimester ultrasound examination in 94.2% of pregnancies. Older (≥35 years old), obese women or women complicated with coexisting medical disorders were more likely to undergo CDMR prior to 39 gestational weeks (P<0.001). Women with male fetuses or those conceived after assisted reproduction were more likely to undergo CDMR prior to 39 weeks (P<0.001). Conversely, women with medical insurance were less likely to undergo CDMR prior to 39 gestational weeks. . The birthweight of the infants and the prevalence of macrosomia (≥4,000g) increased with higher gestational age at delivery.

Figure 2 and table 2 shows the relationship between timing of cesarean delivery and neonatal outcomes. NICU admission was significantly less likely as gestational age at birth increased from 37 to 39 weeks (with rates of 7.3% at 37 weeks and 2.9% at 39 weeks; P for trend<0.001). Similar trends of

decreasing incidence with greater gestational age were also noted for any adverse respiratory outcome and its components (transient tachypnea of the newborn or respiratory distress syndrome), neonatal infection, hypoglycemia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, hyperbilirubinemia and prolonged hospitalization. There were five neonatal deaths (2 each at 38, 39, and 1 at 40 weeks of gestation) and one intrapartum stillbirth associated with amniotic fluid embolism. We also assessed the outcomes for deliveries performed beyond 39 completed weeks of gestation. Compared to neonates born at 39 gestational weeks, there were significant trends toward an increased incidence of NICU admission for delivery at≥40 weeks of gestation (P =0.011). Similar trends were noted for respiratory complications (P <0.001), hypoglycemia (P <0.001), necrotizing enterocolitis（p=0.003）, hypoxic ischemic encephalopathy (P=0.003) and prolonged neonatal hospitalization (P=0.002).

The incidence of adverse maternal outcomes according to completed week of gestation at delivery is shown in supplemental Table 1. There were no differences in maternal outcomes according to completed week of gestation at delivery.

The trends toward the decreasing incidence of neonatal complications with increasing gestational age at term birth up to 39 weeks of gestation remained significant in analyses adjusted for potential confounders. As compared with births at 39-39 6/7 weeks, births at 37-37 6/7 weeks were associated with an increased risk of adverse respiratory outcome (aOR: 4.82;

95% CI:3.35-6.94), neonatal infection (aOR: 3.68; 95% CI:1.80-7.52), hypoglycemia (aOR:3.85; 95%CI:2.29-6.48), hyperbilirubinemia (aOR:3.50; 95%CI:2.12-5.68), neonatal intensive care admission (aOR: 3.73; 95% CI:2.84-4.89) and prolonged hospitalization (aOR:7.51; 95% CI:5.10-11.07). Births at 38-38 6/7 weeks, 40-40 6/7 weeks, or ⩾41 weeks were also associated with an increased risk of adverse respiratory outcome with corresponding aORs (95% CI) of 2.26(1.71-3.00), 1.97(1.33-2.94) and 2.91(1.80-4.70) respectively. Neonates born at these three gestational weeks were more likely to experience neonatal intensive care admission [aOR:1.38 (1.12-1.69), 1.37(1.05-1.77), and 1.52(1.00-2.31) respectively] and prolonged hospitalization [aOR:1.50(1.05-2.15), 1.87(1.23-2.86), and 2.46(1.32-4.57) respectively].

Discussion

This retrospective cohort study of CDMR at the largest obstetric center in Shanghai, China demonstrates that compared with deliveries at 39 weeks, earlier deliveries were associated with a significantly increased risk of an adverse neonatal outcomes that included respiratory complications, neonatal infection, hypoglycemia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, hyperbilirubinemia, NICU admission and prolonged hospitalization to the NICU. Delivery≥ 40 weeks was also associated with increased rates of neonatal adverse outcomes.

The key strength of this study is that it is a large hospital-based

retrospective cohort study, with data abstracted from electronic medical records. Further, we performed a detailed examination of each woman's record such that the indication for cesarean could be clearly ascertained. IPMCHH's policy requiring a consent form for CDMR made us able to determine truly non-medically indicated pre-labor cesarean deliveries. Confounding by indications may impair results from observational studies., In other such reports, neonates with a higher risk of an adverse outcome may be overestimated in cesarean sections undertaken prior to 39 weeks for indications requiring delivery prior to term. We sought to eliminate this confounder by analyzing cases of CDMR. Importance in the present analysis is the accuracy with which we assigned gestational age. First-trimester ultrasound is routinely used to confirm gestational age in Shanghai, and 94.2% of pregnancies underwent first-trimester ultrasound in our study. Our study has some limitations as noted. First, the study population had a low body mass index and was very homogeneous (99% Han) which strengthened our findings but may limit its applicability to other populations. There were only five neonatal deaths and one intrapartum stillbirth despite the large population studied.

Our results are consistent with previous large size studies that performing elective cesarean sections<39+0 weeks of gestation carries with it a significantly higher overall risk of various poor neonatal outcomes [1-4]. In contrast with Tita et al and Wilmink et al's reports that a higher risk of neonatal

complications with cesarean delivery at 41 weeks or later [1,3], our data showed a significantly higher risk for neonatal morbidity by postponing the cesarean section to 40+0 weeks. This phenomenon could potentially be explained by ethnic differences as they relate to in utero pulmonary development. Patel et al reported the median gestational age of spontaneous delivery was 39 weeks in Blacks and Asians and 40 weeks in white Europeans [9], thus fetal maturation may occur earlier in our population.,

In previous observational studies concerning optimal timing of elective cesarean section, the stillbirth rate was not included because of study design limitations [1-3]. However, the studies after implementation of guidelines limiting elective delivery before 39 weeks of gestation reveal contradictory results on the stillbirth rate [15,16]. In our study, we were able to calculate the stillbirth rates per 1,000 ongoing pregnancies at each particular gestational week in our whole cohort. The stillbirth rates per 1,000 ongoing pregnancies were 0.20, 0.20, 0.26, 0.07 and 0.16 at 37, 38, 39, 40, 41respectively, which is a slightly lower than the stillbirth rate of Asian population reported by Balchin and colleagues [17]. It should be noted that, we could only analyze the stillbirth rate in the whole cohort, rather than the elective CDMR group since many women with a stillbirth will have had a vaginal delivery after a stillbirth, thus making it impossible to distinguish between women who had a stillbirth while waiting for a cesarean section, and women with a planned vaginal delivery who had a stillbirth. Using the stillbirth rate of the entire cohort might therefore

overestimate the stillbirth rate in our low-risk CDMR population. We also observed a higher risk of neonatal complications with cesarean delivery at 40 weeks or later. These findings suggest that in addition to the risk of stillbirth, the risk of neonatal complications may also be increased by delaying elective cesarean delivery beyond 39-39 6/7 weeks of gestation in our population.

Most studies of the timing of elective cesarean section up to now are those of primarily repeat procedures, and other studies only include small proportion of primary procedures such as only 788 cases of CDMR in one study, or the primary procedures might be associated with medical and obstetric indications, making questionable the conclusion that elective cesarean delivery should be performed beyond 39 gestational weeks [1-4,18]. Our study importantly adds to the existing data on this subject and confirms the observation from other areas of the world that waiting until 39 weeks for elective cesarean delivery is advisable. It is an important public health consideration since the elective CD rate is high in China and there is also increasing enthusiasm for CDMR in the western countries.

Conclusion

In summary, we demonstrated that elective cesarean section performed at 39-39 6/7 completed weeks of gestation was associated with better neonatal outcomes than earlier or later delivery in a Chinese population. The risk of stillbirth rate is low waiting until 39 gestational weeks. For women undergoing CDMR, neonatal outcome data suggest that delivery at 39 weeks is optimal

timing.

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Contributors

The first author, Dr Hu mainly contributed to design and critical writing. Drs Liu Cheng and Landon mainly contributed to design, the critical revision and interpretation of the data, the final approval of the version to be published. Dr Shen mainly contributed to the management of the cohort study and data collection.

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Competing interests None Declared.

Ethics approval The study was approved by the ethics review board at International Peace Maternity & Child Healthcare Hospital.No:20140124

Data sharing statement No additional data are available.

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Table 1. The stillbirth rates per 1,000 ongoing pregnancies

Gestational week	Stillbirths(n)	OngoingPregnancies	Rate*(per 1000)
37	16	81,507	0.20
38	15	75,276	0.20
39	14	54,273	0.26
40	2	26,716	0.07
≥41	1	6,176	0.16

* Rate is stillbirths per 1,000 ongoing pregnancies or “fetuses at risk” at the gestational week

Table 2.Baseline and obstetric characteristics of the study subjects

Characteristic	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P Value
Maternal age,y(%)						<0.001
≥35	23.9	19.1	16.1	8.2	6.2	
30~34	33.5	37.8	37.4	40.1	37.5	
25-29	38.2	39.8	42.9	47.7	52.0	
≤24	4.4	3.4	3.6	3.9	4.2	
Insurance (%)	61.9	66.5	72.8	72.5	73.9	<0.001
Married (%)	99.8	99.4	99.6	99.4	99.4	0.160
Body-mass index at first prenatal visit**	24.2±3.4	23.6±3.0	23.3±3.0	23.1±3.1	22.9±3.2	<0.001
Education—y &	14.8±2.7	15.0±2.7	14.9±2.7	15.2±2.8	14.8±2.8	0.003
Assisted conception (%)	8.3	6.2	5.1	2.8	1.5	<0.001

GBS (%)ф	3.7	4.0	3.5	3.7	3.9	0.479
STD (%)§	1.8	1.7	1.6	1.7	1.8	0.986
Complicated with other medical disorders (%)†						<0.001
No	80.1	84.6	86.0	89.2	93.5	
Yes	19.9	15.4	14.0	10.8	6.5	
Birth weight (%)						<0.001
≥4,000（g）	2.1	3.2	5.6	9.8	11.8	
3500~3999(g)	13.3	28.4	39.1	50.6	55.6	
2500~3499（g）	78.7	67.9	55.1	39.5	32.5	
<2500(g)	5.8	0.5	0.1	0.1	0.0	
Male sex (%)	54.2	53.5	51.7	50.2	48.6	0.003
First-trimester ultrasound (%)	95.1	94.1	94.2	94.7	93.3	0.356

Plus–minus values are means ±SD.

** body-mass index, is the weight in kilograms divided by the square of the height in meters. Values were missing for 1,196(6.0%) women

& Values were missing for 1,176 (5.9%) women.

ϕ GBS, group B streptococcus . 585(2.9%） women did not undergo this test.

§ STD, sexually transmitted disease. Values were missing for 40(0.2%) women.

† Complicated at least one of cardiac disease, hepatitis, renal disease, DM and GDM, chronic hypertension and gestational hypertension, thyroid disease, preeclampsia, intrahepatic cholestasis of pregnancy.

Table 3. Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery

Outcome	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P for Trend */**
Adverse respiratory outcome						
Respiratory distress syndrome--no(%)	19(1.6)	42(0.6)	19(0.2)	14(0.5)	5(0.6)	<0.001/0.076
Transient tachypnea of the newborn--no(%)	36(3.0)	118(1.6)	55(0.7)	45(1.5)	18(2.2)	<0.001/<0.001
Respiratory complications--no(%)	53(4.5)	154(2.1)	73(1.0)	58(1.9)	23(2.9)	<0.001/<0.001
Neonatal infection--no(%)	12(1.0)	26(0.4)	22(0.3)	17(0.6)	4(0.5)	<0.001/0.103
Hypoxic ischemic encephalopathy--no(‰)	2(1.7)	1(0.1)	1(0.1)	1(0.3)	2(2.5)	0.005/0.003
Meconium aspiration syndrome -no(‰)	1(0.8)	1(0.1)	0	1(0.3)	0(0)	0.055/0.252
Necrotizing enterocolitis -no(‰)	6(5.1)	5(0.7)	1(0.1)	1(0.2)	2(2.5)	<0.001/0.003
Neonate deaths-no(‰)§	0(0)	2(0.3)	2(0.3)	1(0.3)	0(0)	0.712/0.879

Hyperbilirubinemia---no(%)	24(2.0)	54(0.7)	47(0.6)	22(0.7)	4(0.5)	<0.001/0.735
Treated hypoglycemia---no(%)	23(1.9)	59(0.8)	41(0.5)	23(0.7)	16(2.0)	<0.001/<0.001
NICU admission-no(%)	87(7.3)	206(2.9)	165(2.2)	91(3.0)	27(3.4)	<0.001/0.011
Hospitalization ⩾5 days	56(4.7)	71(1.0)	52(0.7)	38(1.2)	13(1.6)	<0.001/0.002

NICU donates neonatal intensive care unit.

*/**The P value was calculated by the Cochran–Armitage test for trend for the period from 37 to 39 weeks/ and from 39 weeks to ≥41 weeks respectively.

§ There were five neonatal deaths, one intrapartum stillbirth due to amniotic fluid embolism during operation

Table 4.Odds Ratios for Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery.*

Outcome odds ratio (95% CI)	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）
Adverse respiratory outcome					
Respiratory distress syndrome	5.94(3.10-11.38)	2.25(1.31-3.88)	Reference	1.98(0.99-3.99)	2.58(0.95-7.04)
Transient tachypnea of the new born	4.41(2.87-6.78)	2.33(1.69-3.21)	Reference	1.97(1.33-2.94)	2.95(1.72-5.08)
Respiratory complications	4.82(3.35-6.94)	2.26(1.71-3.00)	Reference	1.97(1.39-2.79)	2.91(1.80-4.70)
Neonatal infection	3.68(1.80-7.52)	1.30(0.73-2.30)	Reference	2.00(1.06-3.79)	1.87(0.63-5.50)
hyperbilirubinemia	3.50(2.12-5.78)	1.25(0.84-1.85)	Reference	1.19(0.72-1.99)	0.80(0.29-2.23)
Treated hypoglycemia	3.85(2.29-6.48)	1.57(1.05-2.35)	Reference	1.39(0.83-2.32)	3.77(2.09-6.80)
Neonatal intensive care unit admission	3.73(2.84-4.89)	1.38(1.12-1.69)	Reference	1.37(1.05-1.77)	1.52(1.00-2.31)
Hospitalization ⩾5 days	7.51(5.10-11.07)	1.50(1.05-2.15)	Reference	1.87(1.23-2.86)	2.46(1.32-4.57)

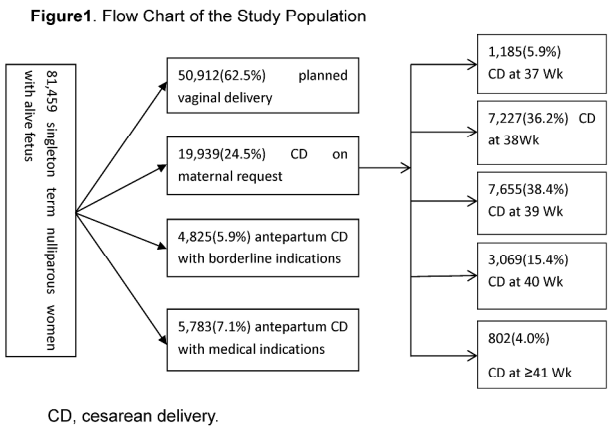
Supplemental Table 1. Adverse Maternal Outcomes According to Completed Week of Gestation at Delivery

Outcome	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P Value for trend
Severe postpartum hemorrhage--no(%)	3(0.3)	27(0.5)	34(0.5)	11(0.4)	1(0.2)	0.545
Maternal infection-no(%)	14(1.4)	67(1.1)	82(1.3)	44(1.7)	6(0.9)	0.568
Maternal organ injury-no(‰)&	0(0)	1(0.2)	2(0.3)	3(1.2)	0(0)	0.960
Embolism-no (‰)§	0	1(0.2)	1(0.2)	1(0.4)	0	-
Mild postpartum hemorrhage-no(%)	20(2.0)	88(1.5)	95(1.5)	46(1.8)	22(3.4)	0.421
Intensive care unit admission-no(%)	2(0.2)	11(0.2)	13(0.2)	5(0.2)	1(0.2)	0.965

* The P value was calculated by the Cochran–Armitage test for trend for the period from 37 to 39 weeks only

&There were four bladder injuries, one ureter injury and one intestinal injury

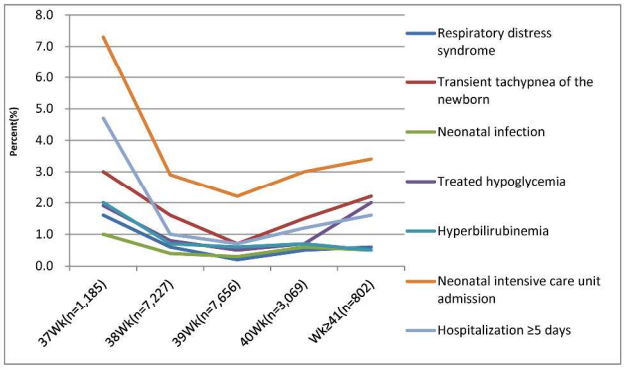
§ There were two pulmonary embolisms and one amniotic fluid embolism



Flow Chart of the Study Population

297x420mm (300 x 300 DPI)

Figure 2. Timing of Cesarean Delivery and Neonatal Outcomes (IPMCHH)



Timing of Cesarean Delivery and Neonatal Outcomes (IPMCHH)

297x420mm (300 x 300 DPI)

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	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	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	
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	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*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	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
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	7-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	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	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
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	14

*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.

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Optimal Timing for Elective Cesarean Delivery in a Chinese Population- a large hospital-based retrospective cohort study in Shanghai

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Optimal Timing for Elective Cesarean Delivery in a Chinese Population- a large hospital-based retrospective cohort study in Shanghai

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Objective: To assess the relationship between the timing of antepartum non-indicated cesarean delivery (CD) at term and perinatal outcomes in a Chinese population.

Methods: We conducted a retrospective cohort study of mode of delivery at a large obstetric center in Shanghai China between 2007-2014. Eligibility criteria included: term nulliparous women with a singleton gestation undergoing antepartum non-indicated CD.

Results: There were 19,939 women delivered by antepartum CD without indications, with 5.9% performed at 37-37 6/7 weeks, 36.2% at 38-38 6/7 weeks, 38.4% at 39-39 6/7 weeks, 15.4% at 40-40 6/7 weeks, 4.0% at ⩾41 weeks. As compared with births at 39-39 6/7 weeks, births at 37 weeks were associated with an increased odds of neonatal respiratory disease (aOR: 4.82; 95% CI:3.35-6.94), neonatal infection (aOR: 3.68; 95% CI:1.80-7.52), hypoglycemia (aOR:3.85; 95%CI:2.29-6.48), hyperbilirubinemia (aOR:3.50; 95%CI:2.12-5.68), neonatal intensive care admission (aOR: 3.73; 95% CI:2.84-4.89) and prolonged hospitalization (aOR:7.51; 95% CI:5.10-11.07). Births at 38 weeks, 40 weeks, or ⩾41 weeks were also associated with an increased odds of neonatal respiratory disease with corresponding aORs (95% CI) of 2.26(1.71-3.00), 1.97(1.33-2.94) and 2.91(1.80-4.70) respectively.

Conclusion: Antepartum non-indicated CD performed at 39-39 6/7 complete weeks was associated with better neonatal outcomes than earlier or later delivery in a Chinese population.

Strengths and limitations

- It is a large hospital-based retrospective cohort study, with data abstracted from electronic medical records. This large population with elective primary CD without indication provides a unique opportunity to find the best timing in relation to neonatal outcomes.
- An important consideration for optimal timing of delivery at term is the ongoing risk of stillbirth with increasing gestational age. In previous observational studies concerning optimal timing of elective cesarean section, the stillbirth rate was not included. In our study, we were able to calculate the stillbirth rates per 1,000 ongoing pregnancies at each particular gestational week in our whole cohort.
- The study population had a low body mass index and was very homogeneous (99% Han) which strengthened our findings but may limit its applicability to other populations.
- There were only five neonatal deaths and one intrapartum stillbirth despite the large population studied. Thus our study was underpowered to analyze the timing of cesarean delivery in relation to the most serious perinatal outcome.

Introduction

Infants born before 39 weeks of gestation are believed to be at increased risk for neonatal adverse respiratory outcomes and a composite adverse neonatal outcome. The risk increases progressively as gestational age at birth declines, especially when the infants are delivered by antepartum cesarean section without labor [1-4]. As a result, national clinical practice guidelines in the UK, the USA, and Canada recommend that planned caesareans should not be performed prior to 39 weeks of gestation without specific indications [5-7]. However, the differences in neonatal outcomes based on gestational age have been reported varies in different race and shorter gestational length has been observed in certain ethnic groups. Some studies suggested that the advantages of waiting until 39 weeks to perform planned cesarean delivery for white women may not be evident in South Asians [8-9]. Without the direct evidence from a Chinese population study, the guideline of waiting to 39 weeks has not been formally implemented in China. The data concerning timing of elective cesarean section has largely come from women undergoing repeat procedures [1,4]. Only few studies have included small proportion of primary procedures [2,3].

China has the highest cesarean delivery (CD) rate in the world. A major reason for the high CD rate is the large proportion of non-indicated cesarean delivery on maternal request (CDMR)[10-13]. "None indication" has actually become the most common reason for CD in most developed areas of China.

Many factors, including the parents' preference of a specific day such as a birth day and physician convenience, have contributed to CD before 39 gestational weeks [10]. There is also increasing enthusiasm for CDMR with a rate of 2.5%~4% in the western countries [14]. The timing of primary elective cesarean delivery has increasingly important public health implications. Therefore, we undertook the present study of a large, retrospective cohort of women to assess the relationship between gestational age at delivery and the risk of adverse perinatal outcomes in a Chinese nulliparous population.

MATERIALS AND METHODS

Study Design

We examined data from all pregnant women receiving care at the International Peace Maternity & Child Healthcare Hospital (IPMCHH), Shanghai Jiaotong University from January 1, 2007 through December 31, 2014. IPMCHH is one of the largest obstetric care centers in Shanghai, with 11,000~ 17,000 annual deliveries with over 90% women being nulliparous due to the Chinese one-child policy which ended in 2015. The study was approved by the ethics review board at IPMCHH.

Study Population

Eligibility criteria for the current study included: nulliparous women with singletons who delivered at term. Those with major fetal anomalies were excluded.

Data Collection

The IPMCHH research group and information engineer extracted and abstracted data from the hospital electronic medical record according to criteria set forth on the standardized data collection form. Types of information that were abstracted include: maternal demographic characteristics, medical history, reproductive and prenatal history, labor and delivery summaries and postpartum and neonatal information. The data were then de-identified prior to analysis.

Antepartum non-indicated CD was defined as an antepartum cesarean section performed either on maternal request or physician preference without medical indications which has been described previously [10]. Cases of antepartum non-indicated CD could be identified in this study as IPMCHH requires that a signed patient consent form outlining the risks and benefits of CD be retained in the medical record. The timing of delivery was determined in completed weeks of gestation such that 37 weeks (for example) included deliveries at 37 0/7–37 6/7 weeks. Gestational age was based on the combination of last menstrual period and first-trimester ultrasound.

The stillbirth rates per 1,000 ongoing pregnancies were calculated in the whole cohort of 81,507eligible women. The following neonatal outcomes calculated in the antepartum non-indicated CD group were studied: neonatal mortality at less than 28 days, respiratory complications (registered as respiratory distress syndrome(RDS), transient tachypnea of the newborn, pneumothorax), hypoglycemia, necrotizing enterocolitis, hypoxic–ischemic

encephalopathy, meconium aspiration syndrome, neonatal infection, hyperbilirubinemia, admission to the neonatal intensive care unit(NICU), and prolonged hospitalization (5 days or longer). The diagnosis of RDS required signs of respiratory distress, consistent radiologic features, and oxygen therapy with a fraction of inspired oxygen (FiO2) of 0.40 or greater for at least 24 hours or until death. Transient tachypnea of the newborn was defined by the presence of tachypnea within hours after birth and typical radiologic findings. The diagnosis of hypoglycemia required a serum or plasma glucose level of less than 2.5 mmol/l or treatment with intravenous glucose. Neonatal infection included pneumonia, sepsis, meningitis or antibiotic management for 3 days or more.

The standardized protocol of the antenatal fetal testing in low-risk pregnancy in Shanghai includes: 1) Non-stressing test begins at 36 gestational weeks, and once a week after; 2) Ultrasound measures with biophysical profile scores is routinely performed at 38 weeks; 3) Obstetricians make a delivery plan with women at 37~38 weeks.

Data were analyzed with the use of SAS software, version 9.2 (SAS Institute, Cary NC). Descriptive statistics included means and standard deviations for continuous variables, and numbers and percentages for categorical variables. The incidence of adverse maternal and neonatal outcomes was calculated for each completed week of gestation at the time of CD. The Cochran–Armitage test for trend was used to assess trends in the

incidence rates of outcomes. Adjusted odds ratios for the association between neonatal outcomes and gestational age at delivery relative to 39 completed weeks of gestation were derived from logistic-regression models that included maternal age, pre-pregnancy body-mass index, education, insurance status, type of conception, maternal chronic medical conditions, and pregnancy complications. A nominal two-sided P value of less than 0.05 was considered statistically significant.

Results

We abstracted data from 98,892 pregnancies to 95,603 unique women that received care at IPMCHH from 2007-2014. After restricting the sample to nulliparous women with singletons who delivered at term, we were left with 81,507 (82.4%) pregnancies to the same number of women for analysis. There were 48 stillbirths after 37^{+0} gestational weeks in this cohort. At 37, 38, 39, 40, 41 gestational weeks, the stillbirth rates per 1,000 ongoing pregnancies were 0.20, 0.20, 0.26, 0.07 and 0.16, respectively (P for GW trend <0.05) (Table 1). In the other 81,459 women with a live fetus, there were 50,912 women who attempted vaginal delivery (spontaneous vaginal birth, assisted vaginal delivery, or intrapartum CD), 10,608 antepartum CD with indications. We identified 19,939 women delivered by antepartum non-indicated CD (Fig. 1). Among the women who underwent antepartum non-indicated CD at term, 5.9% underwent the procedure at 37-37 6/7 weeks, 36.2% at 38-38 6/7 weeks, 38.4% at 39-39 6/7 weeks, 15.4% at 40-40 6/7 weeks and 4.0% at ⩾41 weeks. Thus,

42.1% antepartum non-indicated CD were performed before 39 weeks of gestation.

More than 99% of the women in our study population were of Han ethnicity. Baseline and obstetric characteristics of the study population are shown in Table 2. Gestational age was confirmed by a first- trimester ultrasound examination in 94.2% of pregnancies. Older (≥35 years old), obese women or women complicated with coexisting medical disorders were more likely to undergo CD prior to 39 gestational weeks (P<0.001). Women with male fetuses or those conceived after assisted reproduction were more likely to undergo CD prior to 39 weeks (P<0.001). Conversely, women with medical insurance were less likely to undergo CD prior to 39 gestational weeks. . The birthweight of the infants and the prevalence of macrosomia (≥4,000g) increased with higher gestational age at delivery.

Figure 2 and table 2 shows the relationship between timing of cesarean delivery and neonatal outcomes. NICU admission was significantly less likely as gestational age at birth increased from 37 to 39 weeks (with rates of 7.3% at 37 weeks and 2.9% at 39 weeks; P for trend <0.001). Similar trends of decreasing incidence with greater gestational age were also noted for any adverse respiratory outcome and its components (transient tachypnea of the newborn or respiratory distress syndrome), neonatal infection, hypoglycemia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, hyperbilirubinemia and prolonged hospitalization. There were five neonatal deaths (2

each at 38, 39, and 1 at 40 weeks of gestation) and one intrapartum stillbirth associated with amniotic fluid embolism. We also assessed the outcomes for deliveries performed beyond 39 completed weeks of gestation. Compared to neonates born at 39 gestational weeks, there were significant trends toward an increased incidence of NICU admission for delivery at≥40 weeks of gestation (P =0.011). Similar trends were noted for respiratory complications (P <0.001), hypoglycemia (P <0.001), necrotizing enterocolitis（p=0.003）, hypoxic ischemic encephalopathy (P=0.003) and prolonged neonatal hospitalization (P=0.002).

The incidence of adverse maternal outcomes according to completed week of gestation at delivery is shown in supplemental Table 1. There were no differences in maternal outcomes according to completed week of gestation at delivery.

The risks of neonatal complications were decreased with increasing gestational age at term birth up to 39 weeks of gestation after adjusted for potential confounders. As compared with births at 39-39 6/7 weeks, births at 37-37 6/7 weeks were associated with an increased risk of adverse respiratory outcome (aOR: 4.82; 95% CI:3.35-6.94), neonatal infection (aOR: 3.68; 95% CI:1.80-7.52), hypoglycemia (aOR:3.85; 95%CI:2.29-6.48), hyperbilirubinemia (aOR:3.50; 95%CI:2.12-5.68), neonatal intensive care admission (aOR: 3.73; 95% CI:2.84-4.89) and prolonged hospitalization (aOR:7.51; 95% CI:5.10-11.07). Births at 38-38 6/7 weeks, 40-40 6/7 weeks, or ⩾41 weeks were also associated with an increased risk of adverse respiratory outcome

with corresponding aORs (95% CI) of 2.26(1.71-3.00), 1.97(1.33-2.94) and 2.91(1.80-4.70) respectively. Neonates born at these three gestational weeks were more likely to experience neonatal intensive care admission [aOR:1.38 (1.12-1.69), 1.37(1.05-1.77), and 1.52(1.00-2.31) respectively] and prolonged hospitalization [aOR:1.50(1.05-2.15), 1.87(1.23-2.86), and 2.46(1.32-4.57) respectively].

Discussion

This retrospective cohort study of antepartum non-indicated CD at the largest obstetric center in Shanghai, China demonstrates that compared with deliveries at 39 weeks, earlier deliveries were associated with a significantly increased risk of an adverse neonatal outcomes that included respiratory complications, neonatal infection, hypoglycemia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, hyperbilirubinemia, NICU admission and prolonged hospitalization to the NICU. Delivery≥ 40 weeks was also associated with increased rates of neonatal adverse outcomes.

The key strength of this study is that it is a large hospital-based retrospective cohort study, with data abstracted from electronic medical records. Further, we performed a detailed examination of each woman's record such that the indication for cesarean could be clearly ascertained. IPMCHH's policy requiring a consent form for antepartum non-indicated CD made us able to determine truly non-medically indicated pre-labor cesarean deliveries. Confounding by indications may impair results from observational studies, In

other such reports, neonates with a higher risk of an adverse outcome may be overestimated in cesarean sections undertaken prior to 39 weeks for indications requiring delivery prior to term. We sought to eliminate this confounder by analyzing cases of antepartum non-indicated CD. Importance in the present analysis is the accuracy with which we assigned gestational age. First-trimester ultrasound is routinely used to confirm gestational age in Shanghai, and 94.2% of pregnancies underwent first-trimester ultrasound in our study. Our study has some limitations as noted. First, the study population had a low body mass index and was very homogeneous (99% Han) which strengthened our findings but may limit its applicability to other populations with much higher rates of obesity in which perinatal risks of cesarean may be appreciable. Second, there were only five neonatal deaths and one intrapartum stillbirth despite the large population studied, thus our study was underpowered to analyze the timing of cesarean delivery in relation to the most serious perinatal outcome. Third, only women who successfully had elective cesarean delivery at a certain gestational age were included, the women went into labor or emergency cesarean delivery due to complications before the scheduled date probably bias the results. However, it was reported less than 10% of women went into labor while waiting for delivery at 39 weeks in one clinical trial and the complications were extremely low in this low-risk population, so this bias was unlikely significant [15].

Our results are consistent with previous large size studies that performing

elective cesarean sections<39+0 weeks of gestation carries with it a significantly higher overall risk of various poor neonatal outcomes [1-4]. In contrast with Tita et al and Wilmink et al's reports that a higher risk of neonatal complications with cesarean delivery at 41 weeks or later [1,3], our data showed a significantly higher risk for neonatal morbidity by postponing the cesarean section to 40+0 weeks. This phenomenon could potentially be explained by ethnic differences as they relate to in utero pulmonary development. Patel et al reported the median gestational age of spontaneous delivery was 39 weeks in Blacks and Asians and 40 weeks in white Europeans [9], thus fetal maturation may occur earlier in our population. So we speculate that the 40+0 weeks is kind of post-term for our population, the placenta begins to age and more chance of meconium staining of the amniotic fluid (18% in 39 weeks, 21% in 40 weeks in present study, data not shown). A study compared delivery at each gestational age at term vs. expectant management identified 39 weeks as the optimal timing of delivery, which also supports our findings [4].

An important consideration for optimal timing of delivery at term is the ongoing risk of stillbirth with increasing gestational age. In previous observational studies concerning optimal timing of elective cesarean section, the stillbirth rate was not included because of study design limitations [1-3]. One report suggested that a policy limiting elective delivery before 39 weeks was coincided with an increase in the risks of stillbirths at 37-38 weeks [16]. However, further evaluations of stillbirth trends in US population-based have

not shown an association between increasing gestational age at term and stillbirth [17,18]. In our study, we were able to calculate the stillbirth rates per 1,000 ongoing pregnancies at each particular gestational week in our whole cohort. The stillbirth rates per 1,000 ongoing pregnancies were 0.20, 0.20, 0.26, 0.07 and 0.16 at 37, 38, 39, 40, 41respectively, which is lower than 0.2 of 1000 births at 37 weeks and 0.5 of 1000 births at 38 weeks among Scottish and Canadian, which could be attributed to different local practices of antenatal monitoring , low risk pregnancy included in present study, also could be the lower BMI in our population since it is generally accepted that obesity is associated with increased risk of stillbirth [19]. It should be noted that, we could only analyze the stillbirth rate in the whole cohort, rather than the antepartum non-indicated CD group since many women with a stillbirth will have had a vaginal delivery after a stillbirth, thus making it impossible to distinguish between women who had a stillbirth while waiting for a cesarean section, and women with a planned vaginal delivery who had a stillbirth. Using the stillbirth rate of the entire cohort might therefore overestimate the stillbirth rate in our low-risk antepartum non-indicated CD population. On the basis of stillbirth rate in our population, we estimate 4-5 stillbirths every 10,000 deliveries waiting from 37 weeks to 39 weeks. However, as compared with delivery at 39 weeks, delivery at 37 weeks increased the rate of adverse neonatal outcomes including 140 extra cases of respiratory distress syndrome, 51 necrotizing enterocolitis, 70 neonatal infection, 16 hypoxic ischemic encephalopathy, 510

admissions to the NICU regardless the long- term adverse infant outcomes of early term births [20,21]. We also observed a higher risk of neonatal complications with cesarean delivery at 40 weeks or later. These findings suggest that in addition to the risk of stillbirth, the risk of neonatal complications may also be increased by delaying elective cesarean delivery beyond 39-39 6/7 weeks of gestation in our population.

Most studies of the timing of elective cesarean section up to now are those of primarily repeat procedures, and other studies only include small proportion of primary procedures such as only 788 cases of antepartum non-indicated CD in one study, or the primary procedures might be associated with medical and obstetric indications, making questionable the conclusion that elective cesarean delivery should be performed beyond 39 gestational weeks [1-4, 22]. Our study importantly adds to the existing data on this subject and confirms the observation from other areas of the world that waiting until 39 weeks for elective cesarean delivery is advisable [23]. Since more than 25% of primary cesarean deliveries are performed before the onset of labor in other countries and even much higher in China, and since there may be increasing enthusiasm for cesarean delivery on maternal request in western countries, the timing of primary cesarean delivery and its effect on infant outcomes have substantial public health importance [14, 24].

Conclusion

In summary, we demonstrated that elective cesarean section performed at

39-39 6/7 completed weeks of gestation was associated with better neonatal outcomes than earlier or later delivery in a Chinese population. The risk of stillbirth rate is low waiting until 39 gestational weeks. For women undergoing antepartum non-indicated CD, neonatal outcome data suggest that delivery at 39 weeks is optimal timing.

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Contributors

The first author, Dr Hu mainly contributed to design and critical writing. Drs Liu Cheng and Landon mainly contributed to design, the critical revision and interpretation of the data, the final approval of the version to be published. Dr Shen mainly contributed to the management of the cohort study and data collection.

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Competing interests None Declared.

Ethics approval The study was approved by the ethics review board at

International Peace Maternity & Child Healthcare Hospital.No:20140124

Data sharing statement No additional data are available.

Reference

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Table 1. The stillbirth rates per 1,000 ongoing pregnancies

Gestational week	Stillbirths(n)	OngoingPregnancies	Rate*(per 1000)
37	16	81,507	0.20
38	15	75,276	0.20
39	14	54,273	0.26
40	2	26,716	0.07
≥41	1	6,176	0.16

* Rate is stillbirths per 1,000 ongoing pregnancies or “fetuses at risk” at the gestational week

Table 2.Baseline and obstetric characteristics of the study subjects

Characteristic	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P Value
Maternal age,y(%)						<0.001
≥35	23.9	19.1	16.1	8.2	6.2	
30~34	33.5	37.8	37.4	40.1	37.5	
25-29	38.2	39.8	42.9	47.7	52.0	
≤24	4.4	3.4	3.6	3.9	4.2	
Insurance (%)	61.9	66.5	72.8	72.5	73.9	<0.001
Married (%)	99.8	99.4	99.6	99.4	99.4	0.160
Body-mass index at first prenatal visit**	24.2±3.4	23.6±3.0	23.3±3.0	23.1±3.1	22.9±3.2	<0.001
Education—y &	14.8±2.7	15.0±2.7	14.9±2.7	15.2±2.8	14.8±2.8	0.003
Assisted conception (%)	8.3	6.2	5.1	2.8	1.5	<0.001

GBS (%)ф	3.7	4.0	3.5	3.7	3.9	0.479
STD (%)§	1.8	1.7	1.6	1.7	1.8	0.986
Complicated with other medical disorders (%)†						<0.001
No	80.1	84.6	86.0	89.2	93.5	
Yes	19.9	15.4	14.0	10.8	6.5	
Birth weight (%)						<0.001
≥4,000（g）	2.1	3.2	5.6	9.8	11.8	
3500~3999(g)	13.3	28.4	39.1	50.6	55.6	
2500~3499（g）	78.7	67.9	55.1	39.5	32.5	
<2500(g)	5.8	0.5	0.1	0.1	0.0	
Male sex (%)	54.2	53.5	51.7	50.2	48.6	0.003
First-trimester ultrasound (%)	95.1	94.1	94.2	94.7	93.3	0.356

Plus–minus values are means ±SD.

** body-mass index, is the weight in kilograms divided by the square of the height in meters. Values were missing for 1,196(6.0%) women

& Values were missing for 1,176 (5.9%) women.

ф GBS, group B streptococcus . 585(2.9%） women did not undergo this test.

§ STD, sexually transmitted disease. In Shanghai, syphilis, gonorrhea and chlamydia are routinely tested. Values were missing for 40(0.2%) women.

† Complicated at least one of cardiac disease, hepatitis, renal disease, DM and GDM, chronic hypertension and gestational hypertension, thyroid disease, preeclampsia, intrahepatic cholestasis of pregnancy.

Table 3. Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery

Outcome	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P for Trend */**
Adverse respiratory outcome						
Respiratory distress syndrome--no(%)	19(1.6)	42(0.6)	19(0.2)	14(0.5)	5(0.6)	<0.001/0.076
Transient tachypnea of the newborn--no(%)	36(3.0)	118(1.6)	55(0.7)	45(1.5)	18(2.2)	<0.001/<0.001
Respiratory complications--no(%)	53(4.5)	154(2.1)	73(1.0)	58(1.9)	23(2.9)	<0.001/<0.001
Neonatal infection--no(%)	12(1.0)	26(0.4)	22(0.3)	17(0.6)	4(0.5)	<0.001/0.103
Hypoxic ischemic encephalopathy--no(‰)	2(1.7)	1(0.1)	1(0.1)	1(0.3)	2(2.5)	0.005/0.003
Meconium aspiration syndrome -no(‰)	1(0.8)	1(0.1)	0	1(0.3)	0(0)	0.055/0.252
Necrotizing enterocolitis -no(‰)	6(5.1)	5(0.7)	1(0.1)	1(0.2)	2(2.5)	<0.001/0.003

Neonate deaths-no(‰)§	0(0)	2(0.3)	2(0.3)	1(0.3)	0(0)	0.712/0.879
Hyperbilirubinemia---no(%)	24(2.0)	54(0.7)	47(0.6)	22(0.7)	4(0.5)	<0.001/0.735
Treated hypoglycemia---no(%)	23(1.9)	59(0.8)	41(0.5)	23(0.7)	16(2.0)	<0.001/<0.001
NICU admission-no(%)	87(7.3)	206(2.9)	165(2.2)	91(3.0)	27(3.4)	<0.001/0.011
Hospitalization ⩾5 days	56(4.7)	71(1.0)	52(0.7)	38(1.2)	13(1.6)	<0.001/0.002

NICU donates neonatal intensive care unit.

*/**The P value was calculated by the Cochran–Armitage test for trend for the period from 37 to 39 weeks/ and from 39 weeks to ≥41 weeks respectively.

§ There were five neonatal deaths, one intrapartum stillbirth due to amniotic fluid embolism during operation

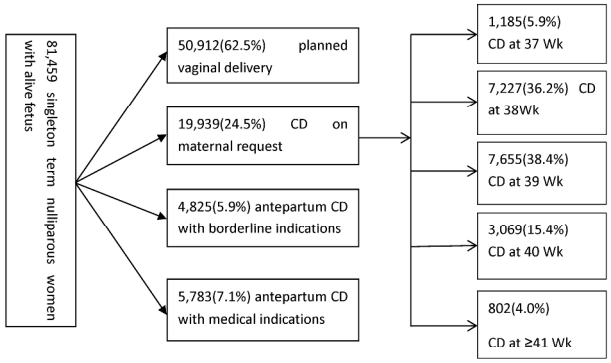
Table 4.Odds Ratios for Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery.*

Outcome odds ratio (95% CI)	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）
Adverse respiratory outcome					
Respiratory distress syndrome	5.94(3.10-11.38)	2.25(1.31-3.88)	Reference	1.98(0.99-3.99)	2.58(0.95-7.04)
Transient tachypnea of the new born	4.41(2.87-6.78)	2.33(1.69-3.21)	Reference	1.97(1.33-2.94)	2.95(1.72-5.08)
Respiratory complications	4.82(3.35-6.94)	2.26(1.71-3.00)	Reference	1.97(1.39-2.79)	2.91(1.80-4.70)
Neonatal infection	3.68(1.80-7.52)	1.30(0.73-2.30)	Reference	2.00(1.06-3.79)	1.87(0.63-5.50)
hyperbilirubinemia	3.50(2.12-5.78)	1.25(0.84-1.85)	Reference	1.19(0.72-1.99)	0.80(0.29-2.23)
Treated hypoglycemia	3.85(2.29-6.48)	1.57(1.05-2.35)	Reference	1.39(0.83-2.32)	3.77(2.09-6.80)
Neonatal intensive care unit admission	3.73(2.84-4.89)	1.38(1.12-1.69)	Reference	1.37(1.05-1.77)	1.52(1.00-2.31)
Hospitalization ⩾5 days	7.51(5.10-11.07)	1.50(1.05-2.15)	Reference	1.87(1.23-2.86)	2.46(1.32-4.57)

The odds ratios were adjusted with maternal age, pre-pregnancy body-mass index, education, insurance status, type of conception,

maternal chronic medical conditions, and pregnancy complications.

Figure1. Flow Chart of the Study Population

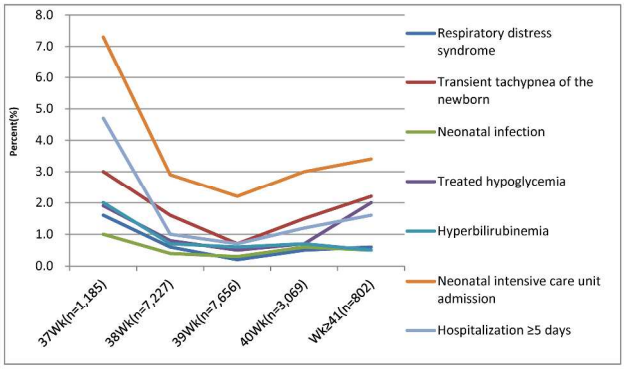


CD, cesarean delivery.

Flow Chart of the Study Population

297x420mm (300 x 300 DPI)

Figure 2. Timing of Cesarean Delivery and Neonatal Outcomes (IPMCHH)



Timing of Cesarean Delivery and Neonatal Outcomes (IPMCHH)

297x420mm (300 x 300 DPI)

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	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	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	
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	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*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	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
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	7-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	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	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
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	14

*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.

Supplemental Table 1. Adverse Maternal Outcomes According to Completed Week of Gestation at Delivery

Outcome	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P Value for trend
Severe postpartum hemorrhage--no(%)	3(0.3)	27(0.5)	34(0.5)	11(0.4)	1(0.2)	0.545
Maternal infection-no(%)	14(1.4)	67(1.1)	82(1.3)	44(1.7)	6(0.9)	0.568
Maternal organ injury-no(‰)&	0(0)	1(0.2)	2(0.3)	3(1.2)	0(0)	0.960
Embolism-no (‰)§	0	1(0.2)	1(0.2)	1(0.4)	0	-
Mild postpartum hemorrhage-no(%)	20(2.0)	88(1.5)	95(1.5)	46(1.8)	22(3.4)	0.421
Intensive care unit admission-no(%)	2(0.2)	11(0.2)	13(0.2)	5(0.2)	1(0.2)	0.965

* The P value was calculated by the Cochran–Armitage test for trend for the period from 37 to 39 weeks only

&There were four bladder injuries, one ureter injury and one intestinal injury

§ There were two pulmonary embolisms and one amniotic fluid embolism

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Optimal Timing for Elective Cesarean Delivery in a Chinese Population- a large hospital-based retrospective cohort study in Shanghai

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Optimal Timing for Elective Cesarean Delivery in a Chinese Population- a large hospital-based retrospective cohort study in Shanghai

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Objective: To assess the relationship between the timing of antepartum elective cesarean delivery (CD) at term and perinatal outcomes in a Chinese population.

Methods: We conducted a retrospective cohort study of mode of delivery at a large obstetric center in Shanghai China between 2007-2014. Eligibility criteria included: term nulliparous women with a singleton gestation undergoing antepartum elective CD.

Results: There were 19,939 women delivered by antepartum CD without indications, with 5.9% performed at 37-37 6/7 weeks, 36.2% at 38-38 6/7 weeks, 38.4% at 39-39 6/7 weeks, 15.4% at 40-40 6/7 weeks, 4.0% at ⩾41 weeks. As compared with births at 39-39 6/7 weeks, births at 37 weeks were associated with an increased odds of neonatal respiratory disease (aOR: 4.82; 95% CI:3.35-6.94), neonatal infection (aOR: 3.68; 95% CI:1.80-7.52), hypoglycemia (aOR:3.85; 95%CI:2.29-6.48), hyperbilirubinemia (aOR:3.50; 95%CI:2.12-5.68), neonatal intensive care admission (aOR: 3.73; 95% CI:2.84-4.89) and prolonged hospitalization (aOR:7.51; 95% CI:5.10-11.07). Births at 38 weeks, 40 weeks, or ⩾41 weeks were also associated with an increased odds of neonatal respiratory disease with corresponding aORs (95% CI) of 2.26(1.71-3.00), 1.97(1.33-2.94) and 2.91(1.80-4.70) respectively.

Conclusion: For women undergoing elective CD, neonatal outcome data suggest that delivery at 39-39 6/7 complete weeks is optimal timing in a Chinese population.

Strengths and limitations

- It is a large hospital-based retrospective cohort study, with data abstracted from electronic medical records. This large population with elective primary CD without indication provides a unique opportunity to determine the optimal timing in relation to neonatal outcomes.
- An important consideration for optimal timing of delivery at term is the ongoing risk of stillbirth with increasing gestational age. In previous observational studies concerning optimal timing of elective cesarean section, the stillbirth rate was not evaluated. In our study, we were able to calculate the stillbirth rates per 1,000 ongoing pregnancies at each particular gestational week in the entire cohort.
- The study population had a low body mass index and was very homogeneous (99% Han) which may limit its generalizability to other populations.
- There were only five neonatal deaths and one intrapartum stillbirth despite the large population studied. Thus our study was underpowered to analyze the timing of cesarean delivery in relation to these serious perinatal outcomes.

Introduction

Infants born before 39 weeks of gestation are believed to be at increased risk for neonatal adverse respiratory outcomes and a composite adverse neonatal outcome. The risk increases progressively as gestational age at birth declines, especially when the infants are delivered by antepartum cesarean section without labor [1-4]. As a result, national clinical practice guidelines in the UK, USA, and Canada recommend that planned cesareans should not be performed prior to 39 weeks of gestation without specific indications [5-7]. However, the differences in neonatal outcomes based on gestational age have been reported varies in different race and shorter gestational length has been observed in certain ethnic groups. Some studies have suggested that the advantages of waiting until 39 weeks to perform planned cesarean delivery for white women may not be evident in South Asians [8-9]. Without the direct evidence from a Chinese population study, the guideline of waiting to 39 weeks has not been formally implemented in China. The data concerning timing of elective cesarean section has largely come from women undergoing repeat procedures [1,4]. Only few studies have included small proportion of primary procedures [2,3].

China has the highest cesarean delivery (CD) rate in the world. A major reason for the high CD rate is the large proportion of elective cesarean delivery on maternal request (CDMR)[10-13]. "None indication" has actually become the most common reason for CD in most developed areas of China. Many

factors, including the parents' preference of a specific day such as a birth day and physician convenience, have contributed to CD before 39 gestational weeks [10]. There is also increasing enthusiasm for CDMR with a rate of 2.5%~4% in the western countries [14]. The timing of primary elective cesarean delivery has increasingly important public health implications. Therefore, we undertook the present study of a large, retrospective cohort of women to assess the relationship between gestational age at delivery and the risk of adverse perinatal outcomes in a Chinese nulliparous population.

MATERIALS AND METHODS

Study Design

We examined data from all pregnant women receiving care at the International Peace Maternity & Child Healthcare Hospital (IPMCHH), Shanghai Jiaotong University from January 1, 2007 through December 31, 2014. IPMCHH is one of the largest obstetric care centers in Shanghai, with 11,000~ 17,000 annual deliveries with over 90% women being nulliparous due to the Chinese one-child policy which ended in 2015. The study was approved by the ethics review board at IPMCHH.

Study Population

Eligibility criteria for the current study included: nulliparous women with singletons who delivered at term. Those with major fetal anomalies were excluded.

Data Collection

The IPMCHH research group and information engineer extracted and abstracted data from the hospital electronic medical record according to criteria set forth on the standardized data collection form. Types of information that were abstracted include: maternal demographic characteristics, medical history, reproductive and prenatal history, labor and delivery summaries and postpartum and neonatal information. The data were then de-identified prior to analysis.

Antepartum elective or non-indicated CD was defined as an antepartum cesarean section performed either on maternal request or physician preference without medical indications which has been described previously [10]. Cases of antepartum elective or non-indicated CD could be identified in this study as IPMCHH requires that a signed patient consent form outlining the risks and benefits of CD be retained in the medical record. The timing of delivery was determined in completed weeks of gestation such that 37 weeks (for example) included deliveries at 37 0/7–37 6/7 weeks. Gestational age was based on the combination of last menstrual period and first-trimester ultrasound.

The stillbirth rates per 1,000 ongoing pregnancies were calculated in the whole cohort of 81,507 eligible women. The following neonatal outcomes calculated in the antepartum non-indicated CD group were studied: neonatal mortality at less than 28 days, respiratory complications (registered as respiratory distress syndrome (RDS), transient tachypnea of the newborn,

pneumothorax, hypoglycemia, necrotizing enterocolitis, hypoxic–ischemic encephalopathy, meconium aspiration syndrome, neonatal infection, hyperbilirubinemia, admission to the neonatal intensive care unit (NICU), and prolonged hospitalization (5 days or longer). The diagnosis of RDS required signs of respiratory distress, consistent radiologic features, and oxygen therapy with a fraction of inspired oxygen (FiO2) of 0.40 or greater for at least 24 hours or until death. Transient tachypnea of the newborn was defined by the presence of tachypnea within hours after birth and typical radiologic findings. The diagnosis of hypoglycemia required a serum or plasma glucose level of less than 2.5 mmol/l or treatment with intravenous glucose. Neonatal infection included pneumonia, sepsis, meningitis or antibiotic management for 3 days or more.

The standardized protocol of the antenatal fetal testing and obstetric management in low-risk pregnancies in Shanghai includes: 1) Non-stress testing at 36 gestational weeks, and weekly thereafter; 2) Ultrasound fetal measurement with biophysical profile scores is routinely performed at 38 weeks; 3) Obstetricians make a delivery plan with women at 37~38 weeks.

Data were analyzed with the use of SAS software, version 9.2 (SAS Institute, Cary NC). Descriptive statistics included means and standard deviations for continuous variables, and numbers and percentages for categorical variables. The incidence of adverse maternal and neonatal outcomes was calculated for each completed week of gestation at the time of

CD. The Cochran–Armitage test for trend was used to assess trends in the incidence rates of outcomes. Adjusted odds ratios for the association between neonatal outcomes and gestational age at delivery relative to 39 completed weeks of gestation were derived from logistic-regression models that included maternal age, pre-pregnancy body-mass index, education, insurance status, type of conception, maternal chronic medical conditions, and pregnancy complications. A nominal two-sided P value of less than 0.05 was considered statistically significant.

Results

We abstracted data from 98,892 pregnancies to 95,603 unique women that received care at IPMCHH from 2007-2014. After restricting the sample to nulliparous women with singletons who delivered at term, we were left with 81,507 (82.4%) pregnancies to the same number of women for analysis. There were 48 stillbirths after 37^{+0} gestational weeks in this cohort. At 37, 38, 39, 40, 41 gestational weeks, the stillbirth rates per 1,000 ongoing pregnancies were 0.20, 0.20, 0.26, 0.07 and 0.16, respectively (P for GW trend <0.05) (Table 1). In the other 81,459 women with a live fetus, there were 50,912 women who attempted vaginal delivery (spontaneous vaginal birth, assisted vaginal delivery, or intrapartum CD), 10,608 antepartum CD with indications. We identified 19,939 women delivered by antepartum elective or non-indicated CD (Fig. 1). Among the women who underwent antepartum non-indicated CD at term, 5.9% underwent the procedure at 37-37 6/7 weeks, 36.2% at 38-38 6/7

weeks, 38.4% at 39-39 6/7 weeks, 15.4% at 40-40 6/7 weeks and 4.0% at ⩾ 41 weeks. Thus, 42.1% antepartum non-indicated CD were performed before 39 weeks of gestation.

More than 99% of the women in our study population were of Han ethnicity. Baseline and obstetric characteristics of the study population are shown in Table 2. Gestational age was confirmed by a first- trimester ultrasound examination in 94.2% of pregnancies. Older (≥35 years old), obese women or women complicated with coexisting medical disorders were more likely to undergo CD prior to 39 gestational weeks (P<0.001). Women with male fetuses or those conceived after assisted reproduction were also more likely to undergo CD prior to 39 weeks (P<0.001). Conversely, women with medical insurance were less likely to undergo CD prior to 39 gestational weeks. The birthweight of the infants and the prevalence of macrosomia (≥4,000g) increased with greater gestational age at delivery.

Figure 2 and Table 3 shows the relationship between timing of cesarean delivery and neonatal outcomes. NICU admission was significantly less likely as gestational age at birth increased from 37 to 39 weeks (with rates of 7.3% at 37 weeks and 2.9% at 39 weeks; P for trend <0.001). Similar trends of decreasing incidence with greater gestational age were also noted for any adverse respiratory outcome and its components (transient tachypnea of the newborn or respiratory distress syndrome), neonatal infection, hypoglycemia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, hyperbilirubinemia

and prolonged hospitalization. There were five neonatal deaths (2 each at 38, 39, and 1 at 40 weeks of gestation) and one intrapartum stillbirth associated with amniotic fluid embolism. We also assessed the outcomes for deliveries performed beyond 39 completed weeks of gestation. Compared to neonates born at 39 gestational weeks, there were significant trends toward an increased incidence of NICU admission for delivery at≥40 weeks of gestation (P =0.011). Similar trends were noted for respiratory complications (P <0.001), hypoglycemia (P <0.001), necrotizing enterocolitis（p=0.003）, hypoxic ischemic encephalopathy (P=0.003) and prolonged neonatal hospitalization (P=0.002).

The incidence of adverse maternal outcomes according to completed week of gestation at delivery is shown in supplemental Table 1. There were no differences in maternal outcomes according to completed week of gestation at delivery.

The risks of neonatal complications were decreased with increasing gestational age at term birth up to 39 weeks of gestation after adjusted for potential confounders (Table 4). As compared with births at 39-39 6/7 weeks, births at 37-37 6/7 weeks were associated with an increased risk of adverse respiratory outcome (aOR: 4.82; 95% CI:3.35-6.94), neonatal infection (aOR: 3.68; 95% CI:1.80-7.52), hypoglycemia (aOR:3.85; 95%CI:2.29-6.48), hyperbilirubinemia (aOR:3.50; 95%CI:2.12-5.68), neonatal intensive care admission (aOR: 3.73; 95% CI:2.84-4.89) and prolonged hospitalization (aOR:7.51; 95% CI:5.10-11.07). Births at 38-38 6/7 weeks, 40-40 6/7 weeks,

or ⩾41 weeks were also associated with an increased risk of adverse respiratory outcome with corresponding aORs (95% CI) of 2.26(1.71-3.00), 1.97(1.33-2.94) and 2.91(1.80-4.70) respectively. Neonates born at these three gestational weeks were more likely to experience neonatal intensive care admission [aOR: 1.38 (1.12-1.69), 1.37(1.05-1.77), and 1.52(1.00-2.31) respectively] and prolonged hospitalization [aOR: 1.50 (1.05-2.15), 1.87(1.23-2.86), and 2.46(1.32-4.57) respectively].

Discussion

This retrospective cohort study of antepartum elective or non-indicated CD at the largest obstetric center in Shanghai, China demonstrates that compared with deliveries at 39 weeks, earlier deliveries were associated with a significantly increased risk of adverse neonatal outcomes. These included respiratory complications, neonatal infection, hypoglycemia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, hyperbilirubinemia, NICU admission and prolonged hospitalization to the NICU. Delivery≥ 40 weeks was also associated with increased rates of neonatal adverse outcomes.

The key strength of this study is that it is a large hospital-based retrospective cohort study, with data abstracted from electronic medical records. Further, we performed a detailed examination of each woman's record such that the indication for cesarean could be clearly ascertained. IPMCHH's policy requiring a consent form for antepartum elective or non-indicated CD made us able to determine truly non-medically indicated pre-labor cesarean

deliveries. Confounding by indicated cesarean deliveries may limit the conclusions drawn from observational studies. In other such reports, the risk of an adverse outcome may be overestimated in cesarean sections undertaken prior to 39 weeks for indications which might be associated with greater neonatal morbidity. We sought to eliminate this confounder by analyzing cases of antepartum CD without indication. Importance in the present analysis is the accuracy with which we assigned gestational age. First-trimester ultrasound is routinely used to confirm gestational age in Shanghai, and 94.2% of pregnancies underwent first-trimester ultrasound in our study. Our study has some limitations as noted. First, the study population had a low body mass index and was very homogeneous (99% Han) which strengthened our findings but may limit its generalizability to other populations with much higher rates of obesity in which perinatal risks of cesarean may be appreciable. Additionally, the stillbirth rate might be different in a population with more obesity as discussed below. Second, there were only five neonatal deaths and one intrapartum stillbirth despite the large population studied, thus our study was underpowered to analyze the timing of cesarean delivery in relation to these serious perinatal outcomes. Third, only women who successfully had elective cesarean delivery at a certain gestational age were included, the women went into labor or emergency cesarean delivery due to complications before the scheduled date might bias the results. However, it was reported less than 10% of women went into labor while waiting for delivery at 39 weeks in one clinical

trial and the complications were extremely low in this low-risk population, so this bias is unlikely to be significant [15]. Fourth, fetal lung maturity testing before elective early-term delivery is not routinely used in China, thus we cannot be certain whether delivery <39 gestational weeks following a positive lung maturity test could reduce the neonatal morbidity prior to 39 weeks.

Our results are consistent with previous large size studies that performing elective cesarean sections<39+0 weeks of gestation carries with it a significantly higher overall risk of various poor neonatal outcomes [1-4]. In contrast with Tita et al and Wilmink et al's reports that found a higher risk of neonatal complications with cesarean delivery at 41 weeks or later [1,3], our data showed a significantly higher risk for neonatal morbidity by postponing the cesarean section to 40+0 weeks. This phenomenon could potentially be explained by ethnic differences as they relate to in utero pulmonary development. Patel et al reported the median gestational age of spontaneous delivery was 39 weeks in Blacks and Asians and 40 weeks in white Europeans [9], thus fetal maturation may occur earlier in our population. So we speculate that 40+0 weeks may be post-term for our population. A study compared delivery at each gestational age at term vs. expectant management identified 39 weeks as the optimal timing of delivery, which also supports our findings [4].

An important consideration for optimal timing of delivery at term is the ongoing risk of stillbirth with increasing gestational age. In previous observational studies concerning optimal timing of elective cesarean section,

the stillbirth rate was not included because of study design limitations [1-3]. One report suggested that a policy limiting elective delivery before 39 weeks coincided with an increase in the risks of stillbirths at 37-38 weeks [16]. However, further evaluations of stillbirth trends in US population-based have not shown an association between increasing gestational age at term and stillbirth [17,18]. In our study, we were able to calculate the stillbirth rates per 1,000 ongoing pregnancies at each particular gestational week in our whole cohort. The stillbirth rates per 1,000 ongoing pregnancies were 0.20, 0.20, 0.26, 0.07 and 0.16 at 37, 38, 39, 40, 41 respectively, which is lower than 0.2 of 1000 births at 37 weeks and 0.5 of 1000 births at 38 weeks among Scottish and Canadian populations. This finding might be attributed to different local practices of antenatal surveillance in low risk pregnancies such as included in present study, also could be secondary to a lower BMI in our population since it is generally accepted that obesity is associated with increased risk of stillbirth [19]. It should be noted that, we could only analyze the stillbirth rate in the whole cohort, rather than the antepartum non-indicated CD group since many women with a stillbirth will have had a vaginal delivery after a stillbirth, thus making it impossible to distinguish between women who had a stillbirth while waiting for a cesarean section, and women with a planned vaginal delivery who had a stillbirth. Using the stillbirth rate of the entire cohort might therefore overestimate the stillbirth rate in our low-risk antepartum non-indicated CD population. On the basis of stillbirth rate in our population, we estimate 4-5

stillbirths every 10,000 deliveries waiting from 37 weeks to 39 weeks. However, as compared with delivery at 39 weeks, delivery at 37 weeks increased the rate of adverse neonatal outcomes including 140 extra cases of respiratory distress syndrome, 51 necrotizing enterocolitis, 70 neonatal infection, 16 hypoxic ischemic encephalopathy, 510 admissions to the NICU regardless the long- term adverse infant outcomes of early term births [20,21]. We also observed a higher risk of neonatal complications with cesarean delivery at 40 weeks or later. These findings suggest that in addition to the risk of stillbirth, the risk of neonatal complications may also be increased by delaying elective cesarean delivery beyond 39-39 6/7 weeks of gestation in our population.

Most studies of the timing of elective cesarean section up to now are those of primarily repeat procedures, and other studies only include small proportion of primary procedures such as only 788 cases of antepartum elective non-indicated CD in one study . Moreover, the primary procedures might be associated with medical and obstetric indications, which might bias the conclusion that elective cesarean delivery should be performed beyond 39 gestational weeks [1-4, 22]. Our study importantly adds to the existing data on this subject and confirms the observation from other areas of the world that waiting until 39 weeks for elective cesarean delivery is advisable [23]. Since more than 25% of primary cesarean deliveries are performed prior to the onset of labor in other countries and even much higher in China, and with increasing enthusiasm for cesarean delivery on maternal request in Western countries,

the timing of primary cesarean delivery and its effect on neonatal outcomes have substantial public health importance [14, 24].

Conclusion

In summary, we demonstrated that elective cesarean section performed at 39-39 6/7 completed weeks of gestation was associated with better neonatal outcomes than earlier or later delivery in a Chinese population. The risk of stillbirth rate is low at term prior to 39 gestational weeks. CDMR should not be recommended, but for women who require elective CD, neonatal outcome data suggest that delivery at 39 weeks is optimal timing.

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Contributors

The first author, Dr Hu mainly contributed to design and critical writing. Drs Liu Cheng and Landon mainly contributed to design, the critical revision and interpretation of the data, the final approval of the version to be published. Dr Shen mainly contributed to the management of the cohort study and data

collection.

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Competing interests None Declared.

Ethics approval The study was approved by the ethics review board at International Peace Maternity & Child Healthcare Hospital.No:20140124

Data sharing statement No additional data are available.

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Table 1. The stillbirth rates per 1,000 ongoing pregnancies

Gestational week	Stillbirths(n)	Ongoing Pregnancies	Rate*(per 1000)
37	16	81,507	0.20
38	15	75,276	0.20
39	14	54,273	0.26
40	2	26,716	0.07
≥41	1	6,176	0.16

* Rate is stillbirths per 1,000 ongoing pregnancies or "fetuses at risk" at the gestational week

Table 2.Baseline and obstetric characteristics of the study subjects

Characteristic	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P Value
Maternal age,y(%)						<0.001
≥35	23.9	19.1	16.1	8.2	6.2	
30~34	33.5	37.8	37.4	40.1	37.5	
25-29	38.2	39.8	42.9	47.7	52.0	
≤24	4.4	3.4	3.6	3.9	4.2	
Insurance (%)	61.9	66.5	72.8	72.5	73.9	<0.001
Married (%)	99.8	99.4	99.6	99.4	99.4	0.160
Body-mass index at first prenatal visit**	24.2±3.4	23.6±3.0	23.3±3.0	23.1±3.1	22.9±3.2	<0.001
Education—y &	14.8±2.7	15.0±2.7	14.9±2.7	15.2±2.8	14.8±2.8	0.003
Assisted conception (%)	8.3	6.2	5.1	2.8	1.5	<0.001

GBS (%)ф	3.7	4.0	3.5	3.7	3.9	0.479
STD (%)§	1.8	1.7	1.6	1.7	1.8	0.986
Complicated with other medical disorders (%)†						<0.001
No	80.1	84.6	86.0	89.2	93.5	
Yes	19.9	15.4	14.0	10.8	6.5	
Birth weight (%)						<0.001
≥4,000（g）	2.1	3.2	5.6	9.8	11.8	
3500~3999(g)	13.3	28.4	39.1	50.6	55.6	
2500~3499（g）	78.7	67.9	55.1	39.5	32.5	
<2500(g)	5.8	0.5	0.1	0.1	0.0	
Male sex (%)	54.2	53.5	51.7	50.2	48.6	0.003
First-trimester ultrasound (%)	95.1	94.1	94.2	94.7	93.3	0.356

Plus–minus values are means ±SD.

** body-mass index, is the weight in kilograms divided by the square of the height in meters. Values were missing for 1,196(6.0%) women

& Values were missing for 1,176 (5.9%) women.

ф GBS, group B streptococcus . 585(2.9%） women did not undergo this test.

§ STD, sexually transmitted disease. In Shanghai, syphilis, gonorrhea and chlamydia are routinely tested. Values were missing for 40(0.2%) women.

† Complicated at least one of cardiac disease, hepatitis, renal disease, DM and GDM, chronic hypertension and gestational hypertension, thyroid disease, preeclampsia, intrahepatic cholestasis of pregnancy.

Table 3. Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery

Outcome	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P for Trend */**
Adverse respiratory outcome						
Respiratory distress syndrome--no(%)	19(1.6)	42(0.6)	19(0.2)	14(0.5)	5(0.6)	<0.001/0.076
Transient tachypnea of the newborn--no(%)	36(3.0)	118(1.6)	55(0.7)	45(1.5)	18(2.2)	<0.001/<0.001
Respiratory complications--no(%)	53(4.5)	154(2.1)	73(1.0)	58(1.9)	23(2.9)	<0.001/<0.001
Neonatal infection--no(%)	12(1.0)	26(0.4)	22(0.3)	17(0.6)	4(0.5)	<0.001/0.103
Hypoxic ischemic encephalopathy--no(‰)	2(1.7)	1(0.1)	1(0.1)	1(0.3)	2(2.5)	0.005/0.003
Meconium aspiration syndrome -no(‰)	1(0.8)	1(0.1)	0	1(0.3)	0(0)	0.055/0.252
Necrotizing enterocolitis -no(‰)	6(5.1)	5(0.7)	1(0.1)	1(0.2)	2(2.5)	<0.001/0.003

Neonate deaths-no(‰)§	0(0)	2(0.3)	2(0.3)	1(0.3)	0(0)	0.712/0.879
Hyperbilirubinemia---no(%)	24(2.0)	54(0.7)	47(0.6)	22(0.7)	4(0.5)	<0.001/0.735
Treated hypoglycemia---no(%)	23(1.9)	59(0.8)	41(0.5)	23(0.7)	16(2.0)	<0.001/<0.001
NICU admission-no(%)	87(7.3)	206(2.9)	165(2.2)	91(3.0)	27(3.4)	<0.001/0.011
Hospitalization ⩾5 days	56(4.7)	71(1.0)	52(0.7)	38(1.2)	13(1.6)	<0.001/0.002

NICU donates neonatal intensive care unit.

*/**The P value was calculated by the Cochran–Armitage test for trend for the period from 37 to 39 weeks/ and from 39 weeks to ≥41 weeks respectively.

§ There were five neonatal deaths, one intrapartum stillbirth due to amniotic fluid embolism during operation

Table 4.Odds Ratios for Adverse Neonatal Outcomes According to Completed Week of Gestation at Delivery.*

Outcome odds ratio (95% CI)	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）
Adverse respiratory outcome					
Respiratory distress syndrome	5.94(3.10-11.38)	2.25(1.31-3.88)	Reference	1.98(0.99-3.99)	2.58(0.95-7.04)
Transient tachypnea of the new born	4.41(2.87-6.78)	2.33(1.69-3.21)	Reference	1.97(1.33-2.94)	2.95(1.72-5.08)
Respiratory complications	4.82(3.35-6.94)	2.26(1.71-3.00)	Reference	1.97(1.39-2.79)	2.91(1.80-4.70)
Neonatal infection	3.68(1.80-7.52)	1.30(0.73-2.30)	Reference	2.00(1.06-3.79)	1.87(0.63-5.50)
hyperbilirubinemia	3.50(2.12-5.78)	1.25(0.84-1.85)	Reference	1.19(0.72-1.99)	0.80(0.29-2.23)
Treated hypoglycemia	3.85(2.29-6.48)	1.57(1.05-2.35)	Reference	1.39(0.83-2.32)	3.77(2.09-6.80)
Neonatal intensive care unit admission	3.73(2.84-4.89)	1.38(1.12-1.69)	Reference	1.37(1.05-1.77)	1.52(1.00-2.31)
Hospitalization ⩾5 days	7.51(5.10-11.07)	1.50(1.05-2.15)	Reference	1.87(1.23-2.86)	2.46(1.32-4.57)

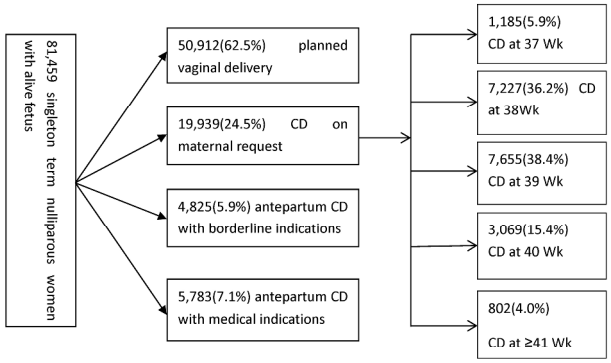
The odds ratios were adjusted with maternal age, pre-pregnancy body-mass index, education, insurance status, type of conception,

maternal chronic medical conditions, and pregnancy complications.

Figure1. Flow Chart of the Study Population

Figure 2. Timing of Cesarean Delivery and Neonatal Outcomes (IPMCHH)

Figure1. Flow Chart of the Study Population

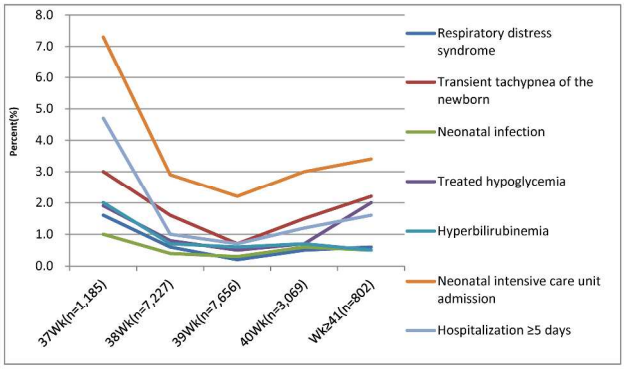


CD, cesarean delivery.

Flow Chart of the Study Population

297x420mm (300 x 300 DPI)

Figure 2. Timing of Cesarean Delivery and Neonatal Outcomes (IPMCHH)



Timing of Cesarean Delivery and Neonatal Outcomes (IPMCHH)

297x420mm (300 x 300 DPI)

Supplemental Table 1. Adverse Maternal Outcomes According to Completed Week of Gestation at Delivery

Outcome	Wk37 (n=1,185)	Wk38 (n=7,227)	Wk39 (n=7,656)	Wk40 (n=3,069)	Wk≥41 (n=802）	P Value for trend
Severe postpartum hemorrhage--no(%)	3(0.3)	27(0.5)	34(0.5)	11(0.4)	1(0.2)	0.545
Maternal infection-no(%)	14(1.4)	67(1.1)	82(1.3)	44(1.7)	6(0.9)	0.568
Maternal organ injury-no(‰)&	0(0)	1(0.2)	2(0.3)	3(1.2)	0(0)	0.960
Embolism-no (‰)§	0	1(0.2)	1(0.2)	1(0.4)	0	-
Mild postpartum hemorrhage-no(%)	20(2.0)	88(1.5)	95(1.5)	46(1.8)	22(3.4)	0.421
Intensive care unit admission-no(%)	2(0.2)	11(0.2)	13(0.2)	5(0.2)	1(0.2)	0.965

* The P value was calculated by the Cochran–Armitage test for trend for the period from 37 to 39 weeks only

&There were four bladder injuries, one ureter injury and one intestinal injury

§ There were two pulmonary embolisms and one amniotic fluid embolism

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	1-2
		(*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	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
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	6
		(*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	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
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	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*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	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
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	8-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	10-11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	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	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,15-16
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	17

*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.