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Original Article

Obstetric outcomes of twin pregnancies at advanced maternal age: A retrospective study

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ABSTRACT

Objective: To evaluate obstetric outcomes in twin pregnancies of advanced maternal age (≥35 years).
Materials and methods: A retrospective study involved 470 twin pregnancies in a single center from Sep. 1, 2012 to Mar. 31, 2015. Clinical characteristics and obstetric outcomes were recorded and compared among twin pregnancies who were classified as follows: age 20–29, 30–34, 35–39 and ≥40 years.
Results: The incidence of gestational diabetes (age 20–29 years 15.8%; 30–34 years 24.3%; 35–39 years 30.4%; ≥40 years 57.1%; $p = 0.004$) and premature delivery (20–29 years 58.6%; 30–34 years 69.1%; 35–39 years 72.2%; ≥40 years 85.7%; $p = 0.001$) significantly increased with increasing age whereas spontaneous abortion (20–29 years 27.6%; 30–34 years 11.6%; 35–39 years 11.4%; ≥40 years 0.0%; $p = 0.021$) decreased in twin pregnancies of advanced maternal age. In addition, the rate of postpartum hemorrhage increased almost continuously by age and advanced maternal age was described as a risk factor for postpartum hemorrhage (age 35–39, adjusted OR 3.377; 95% confidence interval 1729–6.598; $p < 0.001$; age ≥ 40, adjusted OR 10.520; 95% CI 1.147–96.492; $p = 0.037$). However, there was no significant difference between advanced maternal age and adverse neonatal outcomes.
Conclusion: In twin pregnancies, advanced maternal age experienced significant higher risk of postpartum hemorrhage, gestational diabetes and premature delivery. Neither adverse neonatal outcomes nor stillbirth was significantly associated with maternal age.

Introduction

The incidence of twin gestation has risen over the past decades in China, owing to the use of assisted reproductive technology (ART), and is associated with high rate of stillbirth and prematurity [1]. Infants born from twin pregnancies consist approximately 20.0% of perinatal and neonatal morbidity and mortality [2]. It is well known that monochorionic-diamniotic (MCDA) twins represent higher rate of neonatal morbidity than dichorionic-diamniotic (DCDA) twins, which is attributed to placental vascular complications, selective intrauterine growth restriction (sIUGR), maternal obstetric complications and perinatal complications in consequence of prematurity [3]. Considering the low incidence of monochorionic-monoamniotic (MCMA) twins, we only focused on DCDA twins and MCDA twins in this study.

Advanced maternal age, defined as being ≥35 years at delivery, is associated with various maternal obstetric complications. Higher incidence of spontaneous abortion, preeclampsia, preterm delivery and stillbirth in singleton pregnancies who aged ≥35 years [4]. It is well known that advanced maternal age was identified as an independent risk factor for perinatal complications in singleton pregnancy [5]. To date, much fewer studies focused on twin pregnancies aged ≥35 years. Accumulating evidences based on singleton pregnancy. Consequently, the effect of advanced maternal age on twin pregnancies is still unclear.

Recently, there is a consistent trend towards delayed childbearing in China. Management of twin pregnancies at advanced maternal age remains a challenge in obstetric practice. The purpose of this study was to investigate the associations between maternal age and risk maternal–fetal outcomes in twin pregnancies.

Abbreviations: ART, Assisted reproductive technology; MCDA, Monochorionic-diamniotic; DCDA, Dichorionic-diamniotic; sIUGR, Selective intrauterine growth restriction; PROM, Premature rupture of membrane; GDM, Gestational diabetes mellitus; NICU, Neonatal intensive care unit; RDS, Respiratory distress syndrome; NEC, Necrotizing enterocolitis.

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Materials and methods

This was a retrospective cohort study of patients with DCDA twins and MCDA twins at a single tertiary center between Sep. 1, 2012 and Mar. 31, 2015.

Patients aged over 20 years with twin pregnancies were included in the study.

Exclusion criteria included MCMA twins, multiple gestation, and twin pregnancies who underwent selective fetal termination at the first trimester. Chorionicity of twin gestation was assigned prenatally by ultrasound and was confirmed by the review of placental pathology. The gestation age was determined by the patients' last menstrual period or date of fertilization in cases of assisted reproduction. We excluded pregnant women aged younger than 20 years old and complained with chronic diseases, including chronic hypertension or collage vascular disease. This study reducted in accordance with the appropriate clinical and experimental ethical guidelines and was approved by Committee of the First Affiliated Hospital, Sun Yat-sen University. The study was reported with consent from the pregnancies and their relatives.

A total of 470 twin pregnancies, including 330 DCDA twins and 140 MCDA twins, were enrolled in the study. We divided this population into four groups according to the maternal age: 20–29 years, 30–34 years, 35–39 years and ≥40 years.

The primary outcome was postpartum hemorrhage. In addition, the secondary obstetric outcome included: Selective intrauterine growth restriction (sIUGR), premature rupture of membrane (PROM), premature delivery, preeclampsia, gestational diabetes mellitus (GDM) and stillbirth. sIUGR was defined as estimated fetal weight (EFW) <10th percentile matched for gender and twin gestation in the local population and co-twin with EFW >10th percentile. Stillbirth in this study was defined as two fetus died in uterine.

Neonatal outcomes, including neonatal weight, 1-min Apgar score, admission to the neonatal intensive care unit (NICU) rate and incidence of adverse neonatal outcomes, were examined only in the pregnancies who delivered two living newborn. Adverse neonatal outcomes contained respiratory distress syndrome (RDS), jaundice, sepsis, neonatal asphyxia, hypoglycemia, necrotizing enterocolitis (NEC) and so on.

Statistic analysis

All analyses were reported using SPSS version 22.0 (IBM SPSS v 22.0, Armonk, NY). The continuous or dichotomous variables were compared between these groups via the one-way ANOVA. Chi-square test and Fisher's exact test were used to compare the categorical viable. Multivariable logistic regression analysis was performed to determine whether maternal age was significantly independent risk of postpartum hemorrhage and adverse neonatal outcomes. A p value of <0.05 was considered significant.

Results

Among 470 twin pregnancies, 203 (43.2%) cases were 20–29 years, 181 (38.5%) cases were 30–34 years, 79 (16.8%) cases were 35–39 years and 7 (1.5%) cases were ≥40 years. The maternal characteristic across age groups (Table 1) presented that high level of education was most frequent in group (age 30–34 years; $p = 0.002$). Assisted reproductive technology (ART) was taken more frequently in group (age 35–39, 81.0%; $p < 0.001$). Furthermore, more DCDA twins were showed in group (age 35–39, 79.7%; $p < 0.001$).

As shown in Table 2, the incidence of GDM significantly increased with increasing age (20–29 years 15.8%; 30–34 years 24.3%; 35–39 years 30.4%; ≥40 years 57.1%; $p = 0.004$), whereas PROM decreased with increasing age (20–29 years 20.7%; 30–34 years 20.4%; 35–39 years 17.7%; ≥40 years 0.0%; $p = 0.553$). In addition, the rate of postpartum hemorrhage increased almost continuously by age: 20–29 years 22.1%; 30–34 years 17.8%; 35–39 years 62.1%; ≥40 years 83.3%; $p < 0.001$. There was no significant difference of risk of stillbirth in different age ($p = 0.133$).

Neonatal outcomes according to maternal age at delivery were presented in Table 3. The groups were similar in term of gestational age and birth weight. Likewise, the incidence of adverse neonatal outcome among different maternal age were similar (20–29 years 34.6%; 30–34 years 30.3%; 35–39 years 34.1%; ≥40 years 33.3%; $p = 0.706$). Neonatal respiratory distress syndrome (RDS) occurred in 40 women aged 20–29 years, 22 women aged 30–34 years and 8

Table 1
Demographic and obstetrical characteristics (N = 470).

Age (years)	20–29 y	30–34 y	35–39 y	≥40 y	p-value
Number	203 (43.2%)	181 (38.5%)	79 (16.8%)	7 (1.5%)	
Education					0.002
Low level	68 (33.5%)	31 (17.1%)	17 (21.5%)	3 (42.9%)	
High level	135 (66.5%)	150 (82.9%)	62 (78.5%)	4 (57.1%)	
Parity					0.212
Nulliparous	154 (75.9%)	132 (72.9%)	51 (64.4%)	6 (85.7%)	
Multiparous	49 (24.1%)	49 (27.1%)	27 (35.4%)	1 (14.3%)	
Conception					
Natural	123 (60.6%)	48 (26.5%)	15 (19.0%)	2 (28.6%)	<0.001
ART*	80 (39.4%)	133 (73.5%)	64 (81.0%)	5 (71.4%)	
Previous cesarean	16 (7.9%)	14 (7.7%)	6 (16.7%)	0 (0.0%)	0.897
Chorionicity					
MCDA#	87 (42.9%)	38 (21.0%)	16 (20.3%)	2 (28.6%)	<0.001
DCDA**	116 (57.1%)	143 (79.0%)	63 (79.7%)	5 (71.4%)	

*ART: assisted reproductive technology; #MCDA: monochorionic-diamniotiic twins; **DCDA: dichorionic-diamniotic twins.

Table 2
Obstetric and clinical outcomes (N = 470).

Age (years)	20–29 y	30–34 y	35–39 y	≥40 y	p-value
Preeclampsia	14 (6.9%)	12 (6.6%)	7 (8.9%)	2 (5.7%)	0.342
GDM*	32 (15.8%)	44 (24.3%)	24 (30.4%)	4 (57.1%)	0.004
sIUGR***	32 (15.8%)	20 (11.0%)	9 (11.4%)	0 (0.0%)	0.360
PROM#	42 (20.7%)	37 (20.4%)	14 (17.7%)	0 (0.0%)	0.553
Stillbirth	14 (6.9%)	6 (3.3%)	1 (1.3%)	0 (0.0%)	0.133
Congenital malformations	24 (11.8%)	11 (6.1%)	13 (16.5%)	1 (14.3%)	0.064
Postpartum hemorrhage	30 (22.1%)	28 (17.8%)	41 (62.1%)	5 (83.3%)	<0.001
Gestational age at delivery					
<28 wk	56 (27.6%)	21 (11.6%)	9 (11.4%)	0 (0.0%)	0.021
28–37 wk	119 (58.6%)	125 (69.1%)	57 (72.2%)	6 (85.7%)	0.001
≥37 wk	28 (13.8%)	35 (19.3%)	13 (16.5%)	1 (14.3%)	0.324

*GDM: gestational diabetes; ***sIUGR: selective intrauterine growth restriction; #PROM: premature rupture of membrane.

Table 3
Neonatal characteristics and outcomes (N = 730).

Age (years)	20–29 y	30–34 y	35–39 y	≥40 y	p-value
Number	272 (37.3%)	314 (43.0%)	132 (18.1%)	12 (1.6%)	
Gestational age (wk)	34.8 ± 0.322	35.5 ± 0.270	35.0 ± 0.253	35.9 ± 0.344	
Birth weight (g)	2194 ± 556.475	2312 ± 403.623	2235 ± 481.238	2362 ± 264.304	0.022
1′Apgar ≤7	19 (7.0%)	13 (4.1%)	12 (9.1%)	0 (0.0%)	0.146
NICU admission	127 (46.7%)	1 40 (44.6%)	65 (49.2%)	7 (58.3%)	0.673
Adverse neonatal outcomes	94 (34.6%)	95 (30.3%)	45 (34.1%)	4 (33.3%)	0.706

women aged 35–39 years. Further, jaundice was observed in 52 women aged 20–29 years, 52 women aged 30–34 years and 12 women aged 35–39 years. In group of 20–29 years, there were 30 cases of sepsis and 16 cases of neonatal asphyxia, which was higher than other groups (30–34 years 4 and 6; 35–39 years 4 and 2). Interesting, none of women aged over 40 years suffered from RDS, jaundice, sepsis and neonatal asphyxia. The rate of 1-min Apgar sore was higher among neonatal in group of age 35–39 years, compared to neonatal at other groups (20–29 years 7.0%; 30–34 years 4.1%; 35–39 years 9.1%; 40 years 0.0%; p = 0.146). Nevertheless, the risk of admission to neonatal intensive care unit (NICU) was higher in group (age 40 years) among newborns (age 20–29 years 46.7%; 30–34 years 44.6%; 35–39 years 49.2%; ≥40 years 58.3%; p = 0.673).

The impact of maternal age was explored on postpartum hemorrhage (Table 4) and adverse neonatal outcome (Table 5) with adjustment for confounding factors. Compared with the reference group (age 20–29 years), the risk of postpartum hemorrhage was not increased at age 30–34 years, while significant the adjusted odds ratio (OR) was showed at age 35 years or older (age 35–39, adjusted OR 3.377; 95% confidence interval 1729–6.598; p < 0.001; age ≥ 40, adjusted OR 10.520; 95% CI 1.147–96.492; p = 0.037). ART (adjusted OR, 1.966; 95% CI, 1.084–3.566; p = 0.026) and GDM (adjusted OR, 1.962; 95% CI, 1.130–3.409; p = 0.017) were significantly independent risk factors for postpartum hemorrhage. Nulliparous, MCDA twins, the incidence of Preeclampsia, PROM, and sIUGR were significantly associated with adverse neonatal outcomes with an adjusted odds ratio of 1.498 (1.031–2.176) for nulliparous, 2.638 (1.672–4.164) for MCDA twins, 2.050 (1.031–3.555) for preeclampsia, 2.638 (1.672–4.164) for PROM, and 2.119 (1.272–3.532) for sIUGR regardless of maternal age.

Table 4
Logistic regression analysis for postpartum hemorrhage (N = 470).

	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Maternal age (year-old)			
20–29 (reference)	1		
30–34	0.557 (0.291–1.066)	0.558 (0.301–1.036)	0.064
35–39	4.309 (2.068–8.977)	3.377 (1.729–6.598)	<0.001
≥40	14.556 (1.433–147.814)	10.520 (1.147–96.492)	0.037
ART*	1.957 (0.943–4.064)	1.966 (1.084–3.566)	0.026
GDM**	1.947 (1.130–3.409)	1.962 (1.130–3.409)	0.017

*ART: Assisted reproductive technology; GDM: gestational diabetes.

Table 5
Logistic regression analysis for adverse neonatal outcome (N = 730).

	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Maternal age (year-old)			
20–29 (reference)	1	–	
30–34	0.790 (0.529–1.180)	–	0.250
35–39	0.790 (0.473–1.316)	–	0.367
≥40	0.857 (0.231–3.176)	–	0.817
Preeclampsia	2.086 (1.181–3.683)	2.050 (1.031–3.555)	0.011

Discussion

The present study demonstrated that advanced maternal age increased the risk of postpartum hemorrhage in twin pregnancies, particular in nulliparous pregnancies. The advanced maternal age was associated with obstetric complications including GDM and premature delivery, whereas adverse neonatal outcomes had no effect on age-related risk estimates in twin pregnancies.

We found significantly increase rate of postpartum hemorrhage in twin pregnancies aged 35 years or older. Further, logistic regression analysis using maternal age at 20–29 years as reference, revealed that maternal age at 35–39 years and ≥40 years were significantly associated with the postpartum hemorrhage in twin pregnancies. Uterine inertia may cause postpartum hemorrhage in twin pregnancies aged ≥35 years [6]. Another potential explanation was the sclerotic lesion in the myometrial arteries in older pregnancies [7]. This encouraging data was reinforced by Bayrampour [8] who confirmed that physiologic changes in myometrium contractility and arteries with age, in turn, resulted in postpartum hemorrhage. This age-related impact on postpartum hemorrhage was similar in nulliparous twin pregnancies. Ulla et al. [9] reported that parity would reduce or eliminate the risk of advanced maternal age, owing to the physiologic adaptations during previous pregnancy. Our findings suggested that careful monitoring of postpartum hemorrhage in twin pregnancies age 35 years.

As far as adverse neonatal outcomes were concerned, no significant differences were presented among different age groups of twin pregnancies. Recently, advanced maternal age was still described as a risk of adverse neonatal outcomes in singleton pregnancy, including neonatal low-birth weight (LBW, <2500 g) [10], small fetus for the gestational age (SGA, <10th%) [11], respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), jaundice, hypothermia, O2 requirement, ventilation and so on [12]. However, Leonarda and colleagues [13] reported that advanced maternal age had no significant effect on neonatal outcomes except congenital malformations. Our study investigated that 16.5% of twin pregnancies aged 34–39 years and 14.3% of patients aged ≥40 years suffered from congenital malformation, which was consistent with this finding.

Our retrospective study showed that more twin pregnancies aged ≥35 years conceived via ART (p < 0.001) and had DCDA twins (p < 0.001). Despite women's fertility declined with increasing age, more and more pregnancies in advanced maternal age via ART procedure [11].

We found that the prominent contribution of gestational diabetes (GDM, p = 0.004) to maternal morbidity among twin pregnancies aged ≥35 years. Numerous studies investigated that advanced maternal age was a risk of adverse maternal–fetal outcomes including GDM, stillbirth, spontaneous abortion (gestational age at delivery, <28 weeks) and premature delivery (gestational age at delivery, 28–36 + 6 weeks) in singleton pregnancy [14–16]. As we expected, we found a higher incidence of premature delivery (20–29 years 58.6%; 30–34 years 69.1%; 35–39 years 72.2%; ≥40 years 85.7%; p = 0.001) in twin pregnancies with advanced maternal age. In fact, there was a moderating trend of stillbirth

(20–29 years 6.9%; 30–34 years 3.3%; 35–39 years 1.3%; ≥40 years 0.0%; p = 0.113) and spontaneous abortion (20–29 years 27.6%; 30–34 years 11.6%; 35–39 years 11.4%; ≥40 years 0.0%; p = 0.021) based on advanced maternal age in twin pregnancies. A potential explanation was that almost older pregnancies underwent ART and had DCDA twins. MCDA twins increased risk of stillbirth [17]. As a retrospective study, the purpose of this study is to demonstrate the impact of advanced maternal age. Although the group of ≥40 years was rare, we could not exclude its effect in twins pregnancy. However, the potential bias among twins pregnancies aged ≥40 years induced by lowest capacity, requires more cases in this group. Further, few twin pregnancies suffered from stillbirth was the limit in this study.

In conclusion, compared to younger patients (age < 35 years), twin pregnancies with advanced maternal age present significantly higher risk of postpartum hemorrhage, GDM and premature delivery. Neither adverse neonatal outcomes nor stillbirth was significantly associated with maternal age.

The limitation of this study was few cases aged at 40 years old and older. Besides, the physiological pathway between maternal age and postpartum hemorrhage in twin pregnancies was not described in this study. In spite of the need for further studies on larger cohorts, our findings suggested that careful monitoring of postpartum hemorrhage and premature delivery benefit the twin pregnancies age ≥35 years.

Conflict of interest

We declare that we have no conflict of interest.

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