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Original Article

Association between Age and Miscarriage in an Assisted Reproductive Technology Population: A 10-Year Cohort Study

Doudou Zhao [1,2], Jie Chen [3], Xiayang Li [3], Zhaofang Li [3], Jingchen Zhang [4], Caixia Gao [4], Wenbo Hong [4], Danmeng Liu [1,2], Wenhao Shi [1,2], *Juanzi Shi [1,2], *Pengfei Qu [1,2,5]

1. *Translational Medicine Center, Northwest Women's and Children's Hospital, Xi'an, Shaanxi, 710061, China*
2. *Assisted Reproduction Center, Northwest Women's and Children's Hospital, Xi'an, Shaanxi, 710003, China*
3. *Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi, 710061, China*
4. *Graduate Department, Xi'an Medical University, Xi'an, Shaanxi, 710021, China*
5. *Central Laboratory, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Chaoyang, Beijing, China*

***Corresponding Authors:** Emails: xinxi3057@163.com, shijuanzi123@126.com

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Abstract

Background: Advanced maternal age decreased success of pregnancy rate in the assisted reproductive technology (ART) treatment. We aimed to investigate the association between age and miscarriages in women who required ART for conception.

Methods: A cohort study was conducted using a 10-year sample of 14,898 pregnancy cycles with ART treatment in Xi'an, China. The effects of women's age on miscarriage were assessed using Poisson regression models. The threshold effect between age and miscarriage was explored through curve fitting.

Results: Compared with lower than 30 years, the risks of early miscarriage and miscarriage were higher in the older age groups (early miscarriage: [35-37 years: RR=1.48, 95% confidence interval (CI): 1.26 to 1.74; ≥38 years: RR=2.25, 95% CI: 1.87 to 2.72]; miscarriage: [35-37 years: RR=1.45, 95%CI: 1.24 to 1.69; ≥38 years: RR=2.17, 95%CI: 1.82 to 2.60]). The nonlinear relationship between age and early miscarriage and miscarriages were observed. The risk of early miscarriage and miscarriage rapidly increased with age after the turning point (age=33 years) (<33 years: [early miscarriage: RR=1.02, 95% CI: 1.00 to 1.04; miscarriage: RR=1.02, 95% CI: 1.00 to 1.03]; ≥33 years: [early miscarriage: RR=1.11, 95% CI: 1.08 to 1.13; miscarriage: RR=1.10, 95% CI: 1.07 to 1.13]).

Conclusion: Among pregnancy cycles undergoing ART, advanced age is associated with higher risk of early miscarriage and miscarriage, and nonlinear relationship between age and early miscarriage and miscarriage were found. More attention should be paid to the risk of pregnant women with older than 33 years in ART treatment.

Keywords: Advanced age; Miscarriage; Assisted reproductive technology; Cohort study; Chinese population

Introduction

With a developed assisted reproductive technology (ART) and an increased number of fertility services providing ART, ART, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has become a common option for the treatment of infertile couple (1). Over

eight million individuals have been conceived using ART worldwide (2). In the Europe and United States, ART pregnancies represent 1 to 5% of all births (3). And the proportion of ART babies born in China was more than 1% (4), compared with spontaneous conception, ART is associated with an increased risk of multiple gestations, miscarriage, congenital malformations, and preterm birth (5-8).

With the fast development of society, the proportion of advanced age pregnant women (age≥35 years old) is increasing. In China, from 2005 to 2016, the average pregnancy age had increased from 28.5 to 30.2 years old, and the proportion of advanced age pregnant women has increased from 6.5% to 17.2% (9). The advanced age of pregnant women was related to pre-pregnancy complications and adverse pregnancy outcomes, such as gestational diabetes, miscarriage, stillbirth, and premature delivery, which might even affect the newborns' long-term development (10-13). The postponing of childbearing age leads to increased infertile couple and ART treatment. The female age was one of the most critical risk factors that determine the success rate of pregnancy and pregnant outcomes (10). Although most studies had shown that women's age decreased success of pregnancy rate in the ART treatment (14, 15). However, implantation and ongoing pregnancy rate is independent of maternal age (16, 17), and the rates of miscarriage (18) and live birth (19) did not differ significantly by age group.

As studies of the relationship between maternal age and miscarriage with ART treatment are inconsistent and limited. The goal of our study was to reveal the impact of maternal age on early miscarriage and miscarriage based on one of the largest retrospective cohort study of pregnant women with ART treatment in China.

Methods

Study design and population

We conducted a retrospective cohort study using 10 years of clinical data (2006–2015) from the ART center at Northwest Women's and Children's Hospital, Xi'an, Shaanxi province, Northwest China. During this time frame, a total of 15,254 pregnancy cycles were conceived with in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment. Thereafter, we excluded 29 pregnancy cycles with missing age, 67 pregnancy cycles with missing pregnancy outcomes, and 260 pregnancy cycles with missing covariates. Consequently, the rate of loss to follow-up amounted to 2.39% and leaving 14,898 pregnancy cycles for data analyses (Fig. 1).

All pregnancy outcomes (including early miscarriage and miscarriage) were collected from the Shaanxi Assisted Reproduction Database. All demographic data and ART treatment data were collected from hospital outpatient medical record system by nurses and clinicians. In addition, the missing data were supplemented by telephone follow-up as far as possible.

Sample size

Based on the estimated miscarriage rate in pregnant women with ART treatment of 14% for maternal age < 35 years old and 18% for maternal age ≥ 35 years old, the test level was set at α=0.05 and the power at 90%. Consequently, this study necessitates a total of 3528 subjects, our existing sample size of 14,898 fully satisfied this requirement.

Definitions of pregnancy age and miscarriage

The main study variable was pregnant age of women with ART treatment. Resident identity cards of China were used where available to confirm age. In this study, pregnancy age was classified as group 1 (<30 years), group 2 (30-34 years), group 3 (35-37 years) and group 4 (≥38 years).

The main primary outcome measures were early miscarriage and miscarriage. Clinical pregnancy was confirmed using ultrasound at 26 days after blastocyst transfer or 28 days after cleavage-stage embryo transfer. Early miscarriage was defined as the loss of pregnancy before 12 gestational weeks. Miscarriage was defined as the loss of pregnancy before 20 gestational weeks.

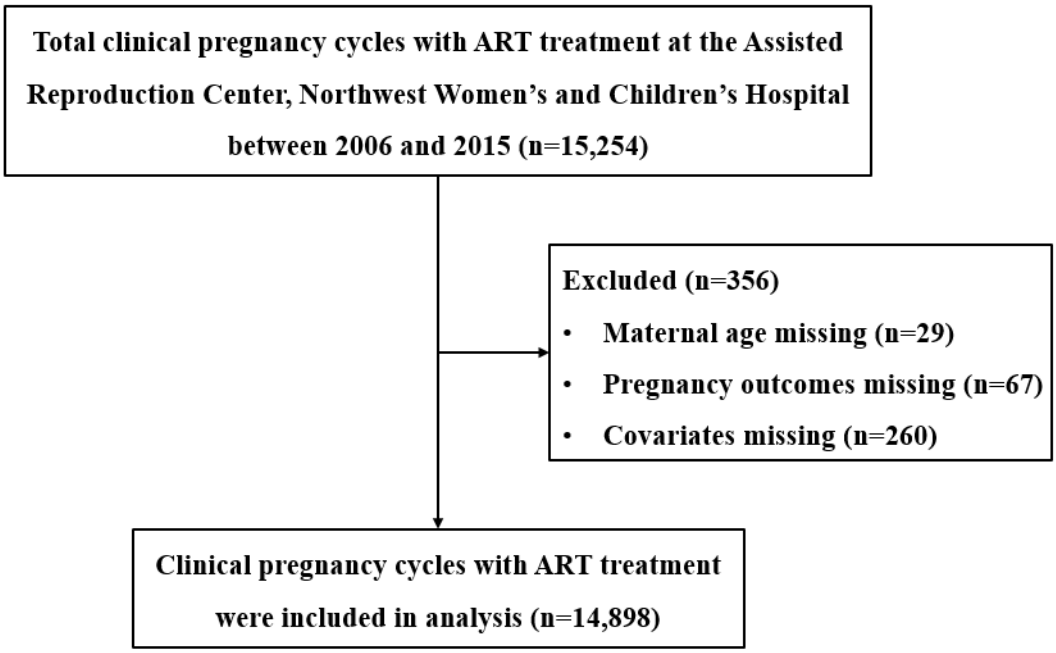

Fig. 1: Eligibility assessment with exclusion criteria

Confounding variables

Potential factors correlated to miscarriage, such as patient baseline demographic characteristics, clinical characteristics, and treatment procedure, were also collected for the study participants. These included BMI before pregnancy (underweight: <18.5 kg/m^2, normal weight: 18.5-23.9 kg/m^2, overweight: 24-27.9 kg/m^2 and obesity: ≥28 kg/m^2), smoking history (yes or no), gravidity (0, 1-2 or ≥3), parity (0 or ≥1), year of transfer(2006-2009, 2010-2012 and 2013-2015), main etiology of infertility (tubal factor, ovarian factor, male factor, and other reasons), fertilization method (IVF, ICSI, IVF + ICSI), sperm donation (yes or no), assisted hatching (yes or no), timing of embryo transfer (fresh embryo transfer or frozen embryo transfer), day 3 or 5 transfer(cleavage stage transfer, blastocyst transfer), antral follicle count, endometrial thickness (mm), basal FSH level (mIU/mL), number of embryos transferred (1 or ≥2) and number of gestational sacs (1 or ≥2).

Statistical analysis

The participants' baseline characteristics are summarized using counts and proportions for categorical variables, and using mean and standard deviation for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables after Kolmogorov-Smirnov test for normality. The chi-squared test or Fisher's exact test was performed to compare categorical variables. Analysis of covariance and the Kruskal–Wallis test were performed to compare normally distributed variables and non-normally distributed variables, respectively.

Poisson regression models were used to assess the effect of age on early miscarriage and miscarriage in three models. We also explored the relationship between age and early miscarriage and miscarriage with a smoothed plot adjusted for all baseline covariates. We further applied a two-piecewise Poisson regression model to examine the threshold effect of age on early miscarriage and miscarriage using a smoothing function. The threshold level was determined using trial and

error, including selection of turning points along a pre-defined interval before choosing the turning point that gave the maximum model likelihood. And likelihood ratio test (LRT test) was used to compare the difference between Model I and Model II (two-piecewise Poisson regression models). We also conducted sensitivity analyses using the Logistic regression models to assess the effect of age on early miscarriage and miscarriage. All statistical analysis in this study was completed through SAS 9.4 software package and Empower (R). A two-tailed *P*-value below 0.05 was considered statistically significant.

Ethics approval

This study was approved by the Human Research Ethics Committee of the Northwest Women's and Children's Hospital (No: 2018002).

Results

Participants' characteristics

A total of 14,898 pregnancy cycles were analyzed in the study. Subjects were divided into four groups (<30, 30-34, 35-37, ≥38 years). The characteristics of participants are presented in Table 1. The older groups were more likely to have higher BMI, gravidity and parity, 2013-2015 transfer, tubal factor infertility, IVF treatment, fresh embryo transfer, assisted hatching, basal FSH level and number of embryos transferred. Finally, the older groups were more likely to have less ICSI treatment, sperm donation, frozen embryo transfer, blastocyst transfer and lower antral follicle count.

Age and early miscarriage

Overall, the rate of early miscarriage was 11.77% among all pregnancy cycles. The rates of early miscarriage varied according to women's age. Among the four groups, the rates of early miscarriage were 10.12%, 11.39%, 15.69%, and 24.89%, respectively (Table 2).

After adjusting for all baseline covariates, group 3 and 4 had 48%, 125% increased risk of early miscarriage relative to the group 1. Additionally, we found statistically significant trend associated between age and early miscarriage (Table 3).

Table 1: Baseline characteristics of pregnancy cycles

Variable	*<30 years (n=7639)*	*30-34 years (n=5181)*	*35-37 years (n=1383)*	*≥38 years (n=695)*	*χ^2/F value*	*P value*
BMI (kg/m²), n (%)					160.860	<0.001
<18.5	880 (11.52)	406 (7.84)	80 (5.78)	29 (4.17)		
18.5-23.9	5245 (68.66)	3486 (67.28)	942 (68.11)	450 (64.75)		
24-27.9	1261 (16.51)	1056 (20.38)	292 (21.11)	180 (25.90)		
≥28	253 (3.31)	233 (4.50)	69 (4.99)	36 (5.18)		
Smoking history, n (%)					6.442	0.081 [a]
No	7615 (99.69)	5168 (99.75)	1374 (99.35)	691 (99.42)		
Yes	24 (0.31)	13 (0.25)	9 (0.65)	4 (0.58)		
Gravidity, n (%)					1290.145	<0.001
0	5253 (68.77)	2667 (51.48)	503 (36.37)	190 (27.34)		
1-2	2114 (27.67)	2050 (39.57)	632 (45.70)	327 (47.05)		
≥3	272 (3.56)	464 (8.96)	248 (17.93)	178 (25.61)		
Parity, n (%)					1606.239	<0.001
0	7412 (97.03)	4663 (90.00)	1038 (75.05)	410 (58.99)		
≥1	227 (2.97)	518 (10.00)	345 (24.95)	285 (41.01)		
Year of transfer, n (%)					35.096	<0.001
2006-2009	513 (6.72)	434 (8.38)	121 (8.75)	48 (6.91)		

Table 1: Continued….

2010-2012	1973 (25.83)	1434 (27.68)	386 (27.91)	153 (22.01)		
2013-2015	5153 (67.46)	3313 (63.95)	876 (63.34)	494 (71.08)		
Main etiology of infertility, n (%)					194.795	<0.001
Tubal factor	3350 (43.85)	2641 (50.97)	785 (56.76)	427 (61.44)		
Ovarian factor	393 (5.14)	257 (4.96)	51 (3.69)	34 (4.89)		
Male factor	1720 (22.52)	874 (16.87)	201 (14.53)	87 (12.52)		
Other reasons	2176 (28.49)	1409 (27.20)	346 (25.02)	147 (21.15)		
Fertilization method, n (%)					65.018	<0.001
IVF	5277 (69.08)	3784 (73.04)	1030 (74.48)	537 (77.27)		
ICSI	2212 (28.96)	1257 (24.26)	317 (22.92)	141 (20.29)		
IVF+ICSI	150 (1.96)	140 (2.70)	36 (2.60)	17 (2.45)		
Sperm donation, n (%)					105.282	<0.001
No	6989 (91.49)	4955 (95.64)	1321 (95.52)	666 (95.83)		
Yes	650 (8.51)	226 (4.36)	62 (4.48)	29 (4.17)		
Assisted hatching, n (%)					700.630	<0.001
No	5805 (75.99)	3879 (74.87)	691 (49.96)	298 (42.88)		
Yes	1834 (24.01)	1302 (25.13)	692 (50.04)	397 (57.12)		
Timing of embryo transfer, n (%)					51.724	<0.001
Fresh embryo transfer	4248 (55.61)	2983 (57.58)	899 (65.00)	438 (63.02)		
Frozen embryo transfer	3391 (44.39)	2198 (42.42)	484 (35.00)	257 (36.98)		
Day 3 or 5, n (%)					94.293	<0.001
Cleavage stage transfer	4742 (62.08)	3410 (65.82)	995 (71.95)	526 (75.68)		
Blastocyst transfer	2897 (37.92)	1771 (34.18)	388 (28.05)	169 (24.32)		
Antral follicle count, median (IQR)	14 (10, 18)	12 (9, 16)	10 (7, 14)	9 (6, 12)	949.830	<0.001 [b]
Endometrial thickness (mm), median (IQR)	10.50 (9.20, 12.00)	10.50 (9.20, 12.00)	10.40 (9.00, 11.90)	10.50 (9.10, 12.00)	4.953	0.175 [b]
Basal FSH level (mIU/mL), median (IQR)	6.49 (5.48, 7.56)	6.54 (5.56, 7.70)	6.81 (5.77, 8.20)	6.98 (5.83, 8.59)	113.560	<0.001 [b]
No. of embryos transferred, n (%)					26.252	<0.001
1	1294 (16.94)	815 (15.73)	216 (15.62)	67 (9.64)		
≥2	6345 (83.06)	4366 (84.27)	1167 (84.38)	628 (90.36)		
No. of gestational sacs [c], n (%)					66.640	<0.001
1	5084 (66.55)	3611 (69.70)	1035 (74.84)	537 (77.27)		
≥2	2555 (33.45)	1570 (30.30)	348 (25.16)	158 (22.73)		

[a] Fisher exact test.
[b] Kruskal-Wallis test.
[c] Determined by ultrasonographic visualization.
BMI, body mass index; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IQR: interquartile range.

Table 2: Association between age and miscarriages in ART pregnancy cycles

Outcomes	*Total (n=14898)*	*<30 years (n=7639)*	*30-34 years (n=5181)*	*35-37 years (n=1383)*	*≥38 years (n=695)*	χ^2	*P value*
Early miscarriage, n (%)	1753(11.77)	773 (10.12)	590 (11.39)	217 (15.69)	173 (24.89)	156.524	<0.001
Miscarriage, n (%)	1905(12.79)	847 (11.09)	636 (12.28)	236 (17.06)	186 (26.76)	165.405	<0.001

Table 3: Effects of age on miscarriages in ART pregnancy cycles: results from the Poisson model analysis

Outcome	*Model 1*	*Model 2* [a]	*Model 3* [b]
	Crude RR (95%CI), P value	Adjusted RR (95%CI), P value	Adjusted RR (95%CI), P value
Early miscarriage			
<30 years	1.0	1.0	1.0
30-34 years	1.13 (1.01, 1.25), 0.031	1.13 (1.02, 1.26), 0.024	1.09 (0.98, 1.22), 0.118
35-37 years	1.55 (1.33, 1.80), <0.001	1.59 (1.36, 1.86), <0.001	1.48 (1.26, 1.74), <0.001
≥38 years	2.46 (2.09, 2.90), <0.001	2.55 (2.13, 3.04), <0.001	2.25 (1.87, 2.72), <0.001
P for trend	<0.001	<0.001	<0.001
Miscarriage			
<30 years	1.0	1.0	1.0
30-34 years	1.11 (1.00, 1.23), 0.052	1.11 (1.00, 1.23), 0.048	1.07 (0.96, 1.19), 0.197
35-37 years	1.54 (1.33, 1.78), <0.001	1.56 (1.35, 1.82), <0.001	1.45 (1.24, 1.69), <0.001
≥38 years	2.41 (2.06, 2.83), <0.001	2.45 (2.07, 2.91), <0.001	2.17 (1.82, 2.60), <0.001
P for trend	<0.001	<0.001	<0.001

[a]Model 2 adjusted BMI before pregnancy, smoking history, gravidity, parity, year of transfer and etiology of infertility.
[b]Model 3 adjusted all baseline variates (BMI before pregnancy, smoking history, gravidity, parity, year of transfer, etiology of infertility, fertilization method, sperm donation, assisted hatching, frozen or fresh embryo transfer, cleavage stage or blastocyst transfer, antral follicle count, endometrial thickness, basal serum FSH, no. of embryos transferred and no. of gestational sacs).

Age and miscarriage

Overall, the rate of miscarriage was 12.79% among all pregnancy cycles. The rates of early miscarriage varied according to women's age. Among the four groups, the rates of early miscarriage were 11.09%, 12.28%, 17.06%, and 26.76%, respectively (Table 2).

After adjusting for all baseline covariates, group 3 and 4 had 45%, 117% increased risk of miscarriage relative to the group 1. Additionally, we found statistically significant trend associated between age and miscarriage (Table 3).

Threshold effects of age on early miscarriage and miscarriage

Figure 2 shows the nonlinear relationship between women's age and early miscarriage and miscarriage, adjusted for baseline covariates. A turning point value of age (age=33 years) was found between age and early miscarriage and miscarriage. The risk of early miscarriage and miscarriage increased by 2% and 2% with one-year increase in age lower than 33 years, but increased by 11% and 10% with one-year increase in age over 33 years. The LRT test demonstrated a non-linear relationship between age and early miscarriage and miscarriage. (Table 4).

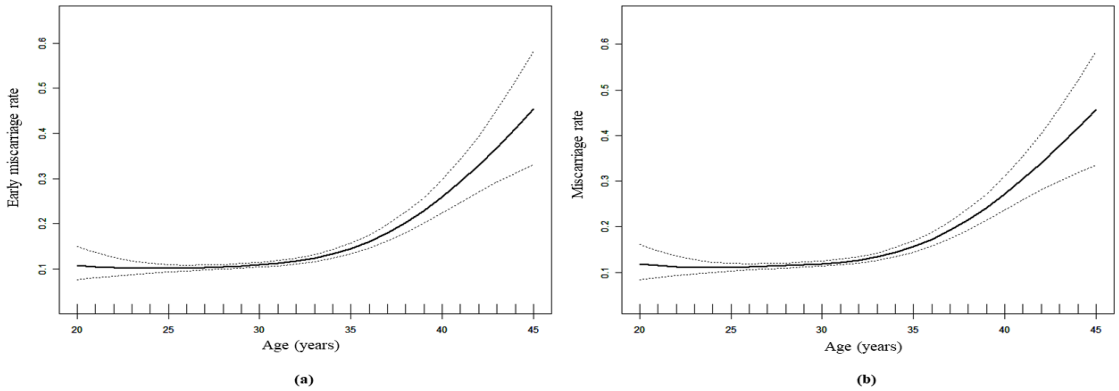

Fig. 2: Smooth curve fitting for the relationship between age and early miscarriages (a) and miscarriages (b) in ART pregnancy cycles. Adjusted all baseline variates.

Table 4: Threshold effects of age on miscarriages in ART pregnancy cycles

Outcome	*Early miscarriage*		*Miscarriage*	
	Crude RR (95%CI), *P* value	Adjusted RR (95%CI)[a], *P* value	Crude RR (95%CI), *P* value	Adjusted RR (95%CI)[a], *P* value
Model I				
One line slope	1.06 (1.05, 1.07), <0.001	1.05 (1.04, 1.06), <0.001	1.02 (1.00, 1.04), <0.001	1.05 (1.03, 1.06), <0.001
Model II				
Turning point (K)	33	33	33	33
<33[b] slope 1	1.02 (1.00, 1.04), 0.029	1.02 (1.00, 1.04), 0.056	1.02 (1.00, 1.04), 0.022	1.02 (1.00, 1.03), 0.065
≥33[b] slope 2	1.12 (1.09, 1.14), <0.001	1.11 (1.08, 1.13), <0.001	1.11 (1.09, 1.14), <0.001	1.10 (1.07, 1.13), <0.001
LRT test	<0.001[c]	<0.001[c]	<0.001[c]	<0.001[c]

[a]Adjusted all baseline variates. [b]Women age as a continuous variable in the two group respectively. [c]*P*<0.05, indicates that Model II is significant different from Model I

Sensitivity analyses

We also assess the effect of age on early miscarriage and miscarriage in explored in the logistic regression models. After adjusting for all baseline covariates, group 3 and 4 had increased risk of early miscarriage and miscarriage than the group 1. Additionally, the threshold effects of age (33 years) on early miscarriage and miscarriage were observed in logistic regression models. (Supplementary Table 1 and 2).

Discussion

Our cohort study, includes a 10-year Chinese sample of 14,898 pregnancy cycles conceived by ART, find that advanced age is associated with higher risk of early miscarriage and miscarriage in ART pregnancy cycles. We also find the nonlinear relationship between age and early miscarriage and miscarriage, and the risk of early miscarriage and miscarriage rapidly increased with age after the turning point in ART pregnancy cycles.

The miscarriage rate of natural conception was reported to be 10-16% (20, 21), and the miscarriage rate of ART conception was as high as 29% (22). In our study, the miscarriage rate of ART pregnancy cycles was 12.79%, and the miscarriage rate of pregnancy cycles with aged 38 years or older reached 26.76%. Previous studies had reported the risk of miscarriage, birth defects,

and chromosomal abnormalities were increased with the increase of maternal age (23, 24). The most common type of triploid spontaneous abortion was closely related to maternal age (25). Our study found that pregnancy cycles with aged 35 years would significantly increase the risk of miscarriage and early miscarriage. Compared with women under 30 years, women aged 36 to 40 years and over 40 years old had a higher risk of early miscarriage (26). Women with the best IVF outcomes were between 20-30 years old, while women aged 40 and over had poor IVF outcomes and a higher miscarriage rate (27).

As the increase of women's age, the ovarian senescence of decline in oocyte yield and quality was the main reason for the poor IVF outcome (28). When a woman reached 30 years old, the fertility decrease became clinically significant and even ART could not compensate for the decline in fertility caused by delayed conception (29). Part of the reason for the decline in fertility and fertilization rate was the decreased follicular reserve and increased aneuploidy in women with advanced age (30, 31). The aneuploidy rate of women at 44 years old could be as high as 53%. In the blastocysts of mothers with advanced age, the transcription of molecular signals that affect embryonic development was reduced, which damaged the embryo's cell signal transduction level, inhibited the proliferation and implantation of the embryo, and caused the deteriorated reproductive results (32).

More than 90% of the miscarriages observed in this study were early miscarriage. Pregnant cycles with 35 years or older would significantly increase the risk of early miscarriage. Studies have shown that early miscarriage and late miscarriage were different. Most early miscarriages were caused by aneuploidy, primarily affected by the mother's age (33). Chromosomal abnormalities would decrease as the pregnancy progresses. Most of them occur before the 12th week of pregnancy (34).

However, this study still had the following shortcomings. First, the fact that retrospective data from a single center were analyzed might weaken the certainty of the conclusions. Additionally, although we used multivariable regressions to control for confounders, the findings may still be subject to unmeasured or hidden confounders because follow-up and data in the hospital information system were limited. Lastly, this study deleted some uncompleted subjects with missing values, resulting in possible selection bias.

Conclusion

Advanced age is associated with higher risk of early miscarriage and miscarriage in pregnancy cycles conceived by ART. The nonlinear relationship between age and early miscarriage and miscarriage are observed. These findings are important for the prevention of adverse pregnant outcomes for pregnant women with ART treatment. The reproductive center staff should pay special attention to the fertility treatment of advanced age women and formulate more personalized treatment plans for the patients according to their conditions. Further verification between maternal age and miscarriage would be needed through high-quality multicenter studies with larger sample sizes in different populations.

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Conflict of Interest

The authors declare that there is no conflict of interests.

References

1. de Mouzon J, Chambers G M, Zegers-Hochschild F, et al (2020). International Committee for Monitoring Assisted Reproductive Technologies world report: assisted reproductive technology 2012†. *Hum Reprod*, 35(8): 1900-1913.
2. Crawford G E, Ledger W L (2019). In vitro fertilisation/intracytoplasmic sperm injection beyond 2020. *BJOG*, 126(2): 237-243.
3. European Society of Human Reproduction and Embryology (2020). ART Fact Sheet. Available at: https://www.eshre.eu/Press-Room/Resources (Accessed 27/01/2021).
4. Yang X, Li Y, Li C, et al (2014). Current overview of pregnancy complications and live-birth outcome of assisted reproductive technology in mainland China. *Fertil Steril*, 101(2): 385-391.
5. Dunietz G L, Holzman C, McKane P, et al (2015). Assisted reproductive technology and the risk of preterm birth among primiparas. *Fertil Steril*, 103(4): 974-979.e1.
6. Sha T, Wang X, Cheng W, et al (2019). A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. *Reprod Biomed Online*, 39(2): 281-293.
7. Wen J, Jiang J, Ding C, et al (2012). Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis. *Fertil Steril*, 97(6): 1331-1337.e1-4.
8. Wilson EE (2005). Assisted reproductive technologies and multiple gestations. *Clin Perinatol*, 32(2): 315-328.
9. Xie M, Lao T T, Du M, et al (2019). Risk for Cesarean section in women of advanced maternal age under the changed reproductive policy in China: A cohort study in a tertiary hospital in southwestern China. *J Obstet Gynaecol Res*, 45(9): 1866-1875.
10. Nybo Andersen AM, Wohlfahrt J, Christens P, et al (2000). Maternal age and fetal loss: population based register linkage study. *BMJ*, 320(7251): 1708-1712.
11. Grande M, Borrell A, Garcia-Posada R, et al (2012). The effect of maternal age on chromosomal anomaly rate and spectrum in recurrent miscarriage. *Hum Reprod*, 27(10): 3109-3117.
12. Pinheiro R L, Areia A L, Mota Pinto A, et al (2019). Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. *Acta Med Port*, 32(3): 219-226.
13. Kahveci B, Melekoglu R, Evruke I C, et al (2018). The effect of advanced maternal age on perinatal outcomes in nulliparous singleton pregnancies. *BMC Pregnancy Childbirth*, 18(1): 343.
14. Hsieh H C, Su J Y, Wang S, et al (2020). Age effect on in vitro fertilization pregnancy mediated by anti-Mullerian hormone (AMH) and modified by follicle stimulating hormone (FSH). *BMC Pregnancy Childbirth*, 20(1): 209.
15. Nelson S M, Lawlor D A (2011). Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles. *PLoS Med*, 8(1): e1000386.
16. Munne S, Mills E, Hill D, et al (2013). Implantation and ongoing pregnancy rate with euploid embryo transfer is independent of maternal age. *Fertil Steril*, 100(3): S131.
17. Irani M, Zaninovic N, Rosenwaks Z, et al (2019). Does maternal age at retrieval influence the implantation potential of euploid blastocysts? *Am J Obstet Gynecol*, 220(4): 379.e1-379.e7.
18. Vitagliano A, Paffoni A, Viganò P (2023). Does maternal age affect assisted reproduction technology success rates after euploid embryo transfer? A systematic review and meta-analysis. *Fertil Steril*, 120(2): 251-265.
19. Reig A, Franasiak J, Scott RT Jr, et al (2020). The impact of age beyond ploidy: outcome data from 8175 euploid single embryo transfers. *J Assist Reprod Genet*, 37(3): 595-602.
20. Assefa N, Berhane Y, Worku A (2013). Pregnancy rates and pregnancy loss in Eastern Ethiopia. *Acta Obstet Gynecol Scand*, 92(6): 642-647.
21. Rossen L M, Ahrens K A, Branum A M (2018). Trends in Risk of Pregnancy Loss Among US Women, 1990-2011. *Paediatr Perinat Epidemiol*, 32(1): 19-29.
22. Farr S L, Schieve L A, Jamieson D J (2007). Pregnancy loss among pregnancies conceived through assisted reproductive technology, United States, 1999-2002. *Am J Epidemiol*, 165(12): 1380-8.
23. Khalil A, Syngelaki A, Maiz N, et al (2013). Maternal age and adverse pregnancy

outcome: a cohort study. *Ultrasound Obstet Gynecol*, 42(6): 634-643.
24. Spandorfer S D, Davis O K, Barmat L I, et al (2004). Relationship between maternal age and aneuploidy in in vitro fertilization pregnancy loss. *Fertil Steril*, 81(5): 1265-1269.
25. Dai R, Li L, Zhu H, et al (2018). Effect of maternal age on spontaneous abortion during the first trimester in Northeast China. *J Matern Fetal Neonatal Med*, 31(14): 1824-1829.
26. Hu L, Du J, Lv H, et al (2018). Influencing factors of pregnancy loss and survival probability of clinical pregnancies conceived through assisted reproductive technology. *Reprod Biol Endocrinol*,16(1):74.
27. Yan J, Wu K, Tang R, et al (2012). Effect of maternal age on the outcomes of in vitro fertilization and embryo transfer (IVF-ET). *Sci China Life Sci*, 55(8): 694-8.
28. Norbert G, Vitaly AK, David FA, et al (2016). Improvements in IVF in women of advanced age. *J Endocrinol*, 230(1): F1-6.
29. Baird D T, Collins J, Egozcue J, et al (2005). Fertility and ageing. *Hum Reprod Update*, 11(3): 261-76.
30. Franasiak J M, Forman E J, Hong K H, et al (2014). The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril*, 101(3): 656-663.e1.
31. Ziebe S, Loft A, Petersen J H, et al (2001). Embryo quality and developmental potential is compromised by age. *Acta Obstet Gynecol Scand*, 80(2): 169-174.
32. McCallie B R, Parks J C, Trahan G D, et al (2019). Compromised global embryonic transcriptome associated with advanced maternal age. *J Assist Reprod Genet*, 36(5): 915-924.
33. Ozawa N, Ogawa K, Sasaki A, et al (2019). Maternal age, history of miscarriage, and embryonic/fetal size are associated with cytogenetic results of spontaneous early miscarriages. *J Assist Reprod Genet*, 36(4): 749-757.
34. Jia C W, Wang L, Lan Y L, et al (2015). Aneuploidy in Early Miscarriage and its Related Factors. *Chin Med J (Engl)*, 128(20): 2772-6.