Jiang *et al. Journal of Ovarian Research* (2025) 18:24
https://doi.org/10.1186/s13048-025-01602-9

Journal of Ovarian Research

RESEARCH Open Access

Maternal age-related declines in live birth rate following single euploid embryo transfer: a retrospective cohort study

Wei Jiang[1], Zichen Zheng[1], Nan Yan[1], Shuang Yao[2], Qijun Xie[1], Danyu Ni[1], Shanren Cao[1], Chun Zhao[1*] and Xiufeng Ling[1*]

Abstract

Purpose To assess whether maternal age influences the pregnancy outcomes after single frozen euploid embryo transfer.

Methods This retrospective analysis was conducted on 1037 cycles of single euploid embryo transfer performed at Nanjing Women and Children's Healthcare Hospital between January 2016 and April 2023. Patients with severe uterine pathologies, immune disorders, or endocrine diseases were excluded. The cycles were categorized into three age groups: <35 years, 35–37 years, and ≥ 38 years. Primary outcomes included live birth rate, clinical pregnancy rate, early pregnancy loss, and miscarriage rate. Data were analyzed using multivariable logistic regression with generalized estimating equations (GEE) to account for confounding factors and restricted cubic splines to visualize the relationship between maternal age and pregnancy outcomes.

Results Women aged ≥ 38 years demonstrated a significantly diminished live birth rate (41.7%) ,which was lower than that observed in women aged < 35 years (54.5%) and 35–37 years (54.0%), with statistical significance ($P < 0.05$). Multivariable regression analysis revealed that compared with women aged ≥ 38 years, younger women had reduced risk of miscarriage (aOR = 0.371, 95% CI: 0.139–0.988 for the < 35 years group; aOR = 0.317, 95% CI: 0.106–0.954 for the 35–37 years group) and increased likelihood of live birth (aOR = 2.188, 95% CI: 1.154–4.147 for the < 35 years group; aOR = 2.239, 95% CI: 1.0103–4.548 for the 35–37 years group) after adjusting for relevant confounders. Additionally, the analysis showed that embryos biopsied on day 5 were linked to higher clinical pregnancy rates than those biopsied on day 6, and high-grade blastocysts were associated with superior pregnancy outcomes.

Conclusion Advanced maternal age is associated with a higher miscarriage rate and lower live birth rate following euploid embryo transfer. Despite the exclusion of aneuploidy, age-related factors beyond chromosomal abnormalities appear to impact reproductive outcomes.

Wei Jiang and Zichen Zheng contributed equally to this work.

*Correspondence:
Chun Zhao
zhaochun2008@yeah.net
Xiufeng Ling
lingxiufeng_njfy@163.com

Full list of author information is available at the end of the article

Keywords Advanced age, Euploid embryos, Miscarriage rate, Live birth rate

Introduction

The decision to postpone childbearing has become increasingly common among women in recent years, driven by evolving social, professional, and cultural factors [1, 2]. This shift, while empowering for women's autonomy, presents significant challenges to female fertility, particularly as maternal age advances [3]. Advanced maternal age is associated with a decline in fertility, evidenced by a three-fold increase in the risk of miscarriage for women over 40 compared to their younger counterparts aged 20–34 [4]. Multiple potential factors have been suggested to explain fecundity declines in women of advanced age, with age-related oocyte aneuploidy considered the most significant determinant [5]. In fact, aneuploidy rates escalate from approximately 25% in women aged 25–30 to over 50% in those over 35, reaching 88.2% by age 44 [6].

Preimplantation genetic testing for aneuploidy (PGT-A) has been adopted to reduce the transfer of aneuploid embryos during assisted reproductive treatment, aiming to enhance implantation rates and reduce miscarriage risk [7, 8]. However, whether the selection of euploid embryos can completely counteract age-related fertility decline and equalize pregnancy outcomes between older and younger women remains controversial.

While some studies suggest that maternal age has a diminished effect on implantation potential once aneuploid embryos are excluded, others report a continued decline in clinical pregnancy and live birth rates with increasing age, indicating that factors beyond aneuploidy may contribute to fertility decline [9–12]. The inconsistency in study outcomes may be attributed to various factors, including differences in blastocyst morphological grading and the indication for PGT, which may bias the overall conclusions.

With all this in mind, the main purpose of this study was to assess whether maternal age can influence assisted reproductive technology (ART) success rates after euploid embryos transfer, accounting for blastocyst morphological grading based on Chinese expert consensus and other confounders such as the indication for PGT [13].

Materials and methods

Cycle selection

All frozen embryo transfer cycles (FET) involving euploid embryos transferred at the reproductive medicine center of Nanjing Women and Children's Healthcare Hospital between January 2016 and April 2023 were reviewed for inclusion. This study was approved by the Institutional Review Board of Nanjing Women and Children's Healthcare Hospital. Single embryo transfer (SET) was utilized in all cycles. Patients with severe uterine pathologies (e.g., moderate to severe intrauterine adhesions or anatomical abnormalities), immune disorders, or endocrine diseases were excluded from the study.

Ovarian stimulation and laboratory protocol

Gonadotropin-releasing hormone (GnRH) antagonist protocol, GnRH agonist, or mild stimulation were administered based on individual patient characteristics, ovarian reserve assessment, and prior response to stimulation. The majority of cycles utilized GnRH antagonist protocol. Exogenous gonadotropins (Gonal-F, EMD-Serono; Follistim, Merck) were administered daily. Once either estradiol (E_2) level exceeded 300 pg/mL or the lead follicle reached 13 mm in diameter, GnRH antagonists (Ganirelix acetate, 0.25 mg, Organon; Cetrotide, 0.25 mg, EMD-Serono) were introduced for pituitary suppression. Oocyte maturation was triggered by administering hCG (Chorionic Gonadotropin for Injection, 5000-10,000 IU, Livzon Pharm) and/or GnRH agonist (Dophereline, 0.2 mg, Ferring) when at least three follicles measured ≥ 17 mm or at least two follicles reached ≥ 18 mm in diameter. Transvaginal ultrasound-guided follicle aspiration was performed 36 h later to retrieve the oocytes, which were fertilized via intracytoplasmic sperm injection (ICSI).

Embryos were cultured either in conventional benchtop incubators or in time-lapse systems. Blastocysts were morphologically graded according to modified Gardner criteria. Blastocysts graded AA, AB, BA, or BB were considered good quality, and BC or CB as average quality according to expert consensus of Chinese [13]. Trophectoderm biopsy was performed on either day 5 or day 6 depending on embryonic development, using a biopsy pipette aspirated 5–10 cells. The comprehensive chromosomal analysis of embryos for PGT-A and Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR) was performed using Next-Generation Sequencing (NGS). Concurrently, karyomapping was performed as part of Preimplantation Genetic Testing for Monogenic Diseases (PGT-M), with an assessment of chromosomal aneuploidy to determine whether the embryo was euploid. The FET was performed if patients who obtained euploid embryos.

Outcome variables assessed

The primary outcome measured was the live birth rate, while secondary outcomes included clinical pregnancy, early pregnancy loss, and miscarriage rates. Live birth rate was defined as the proportion of cycles resulting in at

least one live-born infant delivered after 26 weeks of gestation. Clinical pregnancy rate was defined as the number of cycles with ultrasound-confirmed viable intrauterine pregnancy divided by the total number of cycles. Early pregnancy loss rate was defined as the proportion of clinical pregnancies resulting in missed or miscarriages in the first trimester. Miscarriage rate was defined as the total number of miscarriages before 26 weeks of gestation divided by the total number of cycles with clinical pregnancies. The cycles were divided into three groups according to the maternal age. Outcomes and baseline demographic characteristics were compared among the three groups. The extracted demographic characteristics included age, body mass index (BMI), gravidity, the number of previous miscarriages, the indication for PGT, the subcategories of PGT, peak endometrial thickness, endometrial preparation protocols, day of biopsy, blastocyst morphological grading.

Table 1 Baseline demographics of patients undergoing euploid blastocyst transfer

	< 35	**35–37**	**≥ 38**	
	***n* = 796**	***n* = 126**	***n* = 115**	***P***
Maternal age (y)	29.65 ± 2.90[ab]	35.87 ± 0.79[b]	39.52 ± 1.48	< 0.001
BMI(kg/m^2)	22.13 ± 3.04[ab]	22.85 ± 3.07	23.25 ± 2.83	< 0.001
Gravidity	2.10 ± 1.65[ab]	3.48 ± 1.59	3.24 ± 1.55	< 0.001
Parity	0.40 ± 0.63[ab]	0.78 ± 0.68	0.87 ± 0.63	< 0.001
The number of previous miscarriages	1.34 ± 1.27[a]	2.20 ± 1.42[b]	1.57 ± 1.36	< 0.001
The indication for PGT				< 0.001
Recurrent spontaneous abortion	337 (42.3)	87 (69.0)	32 (27.8)	
Repeated implantation failure	21 (2.6)	3 (2.4)	3 (2.6)	
Advanced maternal age	0 (0.0)	0 (0.0)	72 (62.6)	
Chromosomal structural rearrangements	385 (48.4)	28 (22.2)	7 (6.1)	
Monogenic disorders	53 (6.7)	8 (6.4)	1 (0.9)	
The subcategories of PGT				< 0.001
PGT-A	468 (58.8)	100 (79.4)	108 (93.9)	
PGT-SR	275 (34.6)	18 (14.3)	6 (5.2)	
PGT-M	53 (6.7)	8 (6.3)	1 (0.9)	
Peak endometrial thickness (mm)	9.07 ± 1.54	9.06 ± 1.56	9.03 ± 1.62	0.972
Endometrial preparation protocols				0.015
Natural cycle	97 (12.2)	24 (19.1)	11 (9.6)	
Ovulatory cycle	103 (12.9)	13 (10.3)	6 (5.2)	
Artificial cycle	596 (74.9)	89 (70.6)	98 (85.2)	
Day of biopsy				0.052
D5	470 (59.1)	60 (47.6)	68 (59.1)	
D6	326 (40.9)	66 (52.4)	47 (40.9)	
Morphological grading				0.249
Good (AA/AB/BA/BB)	584 (73.4)	97 (77.0)	92 (80.0)	
Average (BC/CB)	212 (26.6)	29 (23.0)	23 (20.0)	

Data are presented as mean ± standard deviation and n (%)

BMI, body mass index; PGT, preimplantation genetic testing

a, compared with the group of women aged 35–37, $P < 0.05$; b, compared with the group of women aged women aged 38 years and older, $P < 0.05$

Statistical analysis

Statistical analyses were conducted using SPSS version 27.0 and R version 4.3.3. Continuous variables were reported as the mean ± SD, and categorical variables were presented as n (%). Comparisons among different groups were performed with one-way ANOVA, Bonferroni-adjusted test and Chi-square test. Generalized estimating equations (GEE) were performed to evaluate the relationship between the confounding factors, maternal age and pregnancy outcomes after euploid embryos transfer (clinical pregnancy; early pregnancy loss; miscarriage; live birth), as some patients had more than one cycle included in our cohort, and these cycles are not considered independent of each other. The confounding factors included BMI, the number of previous miscarriages, the indications for PGT, endometrial preparation protocols, peak endometrial thickness, day of biopsy and blastocyst morphological grading. The results were presented as adjusted odds ratio (aOR) with 95% CIs and P-value of < 0.05 was considered statistically significant. Finally, we used restricted cubic spline to further visualize the actual relationship between maternal age and pregnancy outcomes.

Results

A total of 1037 cycles of euploid embryo transfer were included for analysis, divided into three groups based on maternal age: <35 years ($n = 796$), 35–37 years ($n = 126$), and ≥ 38 years ($n = 115$). Demographic characteristics and baseline clinical laboratory results are presented in Table 1. Significant differences were observed among the three groups in body mass index (BMI), gravidity, parity and the number of previous miscarriages, the indications for PGT, the subcategories of PGT, and endometrial preparation protocols ($P < 0.05$). Compared to women younger than 35 years, those in the other two age groups exhibited higher BMI values, gravidity and parity. Additionally, women aged 35–37 had a higher proportion of recurrent pregnancy loss compared to the other two groups. No significant differences were observed among the three groups in terms of peak endometrial thickness, day of biopsy, or blastocyst morphological grading.

As shown in Fig. 1, the clinical pregnancy rate among women aged ≥ 38 years were slightly reduced compared

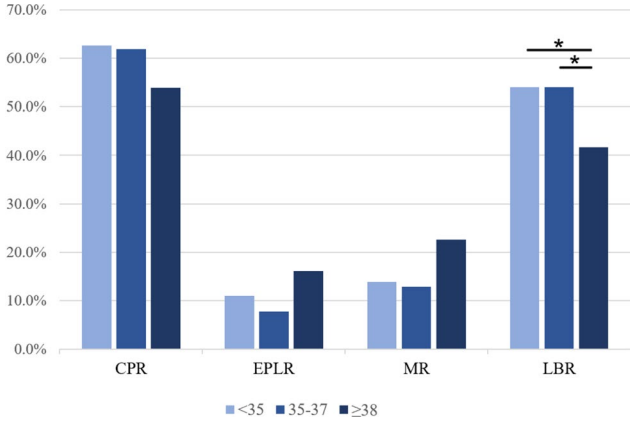

Fig. 1 Pregnancy outcomes in each age group. CPR, Clinical pregnancy rate; EPLR, early pregnancy loss rate; MR, miscarriage rate; LBR, live birth rate. *, $P < 0.05$

to their younger counterparts, with respective rates of 62.7%, 61.9%, and 53.9% ($P = 0.194$). Additionally, the rates of early pregnancy loss (11% vs. 7.7% vs. 16.1%, $P = 0.285$) and miscarriage (13.0% vs. 12.8% vs. 22.6%, $P = 0.117$) showed a modest increase in the older age group, although these differences did not achieve statistical significance. Notably, a significant disparity in live birth rate was observed, with women aged ≥ 38 years showing a substantially lower rate of 41.7% compared to the 54.5% and 54.0% in the younger groups ($P < 0.05$).

Table 2 presents findings from the multivariable logistic regression analyses using GEE. After adjusting for BMI, number of the miscarriage, the indication for PGT, endometrial preparation protocols, peak endometrial thickness, day of biopsy and blastocyst morphological grading, the group with women aged ≥ 38 years exhibited a significant increase in miscarriage rate following euploid embryo transfer compared to the other two groups (aOR = 0.371, 95% CI: 0.139–0.988 for the < 35 years group; aOR = 0.317, 95% CI: 0.106–0.954 for the 35–37 years group). Furthermore, a significantly reduced live birth rate was observed in women aged ≥ 38 years compared to those in the other two age groups (aOR = 2.188, 95% CI: 1.154–4.147 for the < 35 years group; aOR = 2.239, 95% CI: 1.0103–4.548 for the 35–37 years group). Additionally, the differences in the clinical pregnancy rates and early pregnancy loss rates among the three groups were not statistically significant after adjusting for all confounding variables. Notably, embryos biopsied on day 5 were associated with a higher clinical pregnancy rate compared to those biopsied on day 6 (adjusted OR, 1.482; 95% CI, 1.127–1.948; $P = 0.005$), and morphologically high-grade blastocysts demonstrated significantly better pregnancy outcomes than their low-grade counterparts (overall $P < 0.05$).

To further assess the impact of maternal age on pregnancy outcomes following the transfer of euploid embryos, we employed restricted cubic splines for data fitting and analysis. As illustrated in Fig. 2, advancing maternal age was associated with an increased rate of miscarriage and a decreased rate of live birth ($P < 0.05$).

Discussion

The findings of this study demonstrated that an increase in maternal age was associated with a higher miscarriage rate and a lower live birth rate following single euploid embryo transfer. This trend became evident particularly among women aged 38 years and older. By excluding the influence of aneuploidy, our results suggested that age may still exert a detrimental impact on fertility through other biological pathways.

Our findings align with several previous studies reporting a negative association between age and live birth rates [11, 14]. Conversely, some studies have reported that advanced maternal age yields comparable pregnancy outcomes to those of younger women, which contrasts with our findings [9, 10, 15]. The differing results observed in

Table 2 Generalized estimating equation analysis for pregnancy outcomes

	Clinical pregnancy		Early pregnancy loss		Miscarriage		Live birth	
	aOR (95%CI)	*P*	aOR (95%CI)	*P*	aOR (95%CI)	*P*	aOR (95%CI)	*P*
Maternal age (y)								
<35	1.641(0.852,3.162)	0.139	0.662(0.229,1.914)	0.446	0.371(0.139,0.988)	0.047	2.188(1.154,4.147)	0.016
35-37	1.635(0.794,3.365)	0.182	0.407(0.113,1.461)	0.168	0.317(0.106,0.954)	0.041	2.239(1.103,4.548)	0.026
≥38	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Day of biopsy								
D5	1.482(1.127,1.948)	0.005	1.504(0.829,2.732)	0.180	1.525(0.891,2.612)	0.124	1.228(0.945,1.598)	0.125
D6	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Morphological grading								
Good (AA/AB/BA/BB)	1.645(1.208,2.239)	0.002	0.463(0.242,0.886)	0.020	0.503(0.277,0.916)	0.025	1.831(1.361,2.464)	<0.001
Average (BC/CB)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

aOR, adjusted odds ratio; CI, confidence interval; Ref., Reference

Adjusted for age, body mass index, the number of previous miscarriages, the indications for PGT, endometrial preparation protocols, peak endometrial thickness, day of biopsy and blastocyst morphological grading

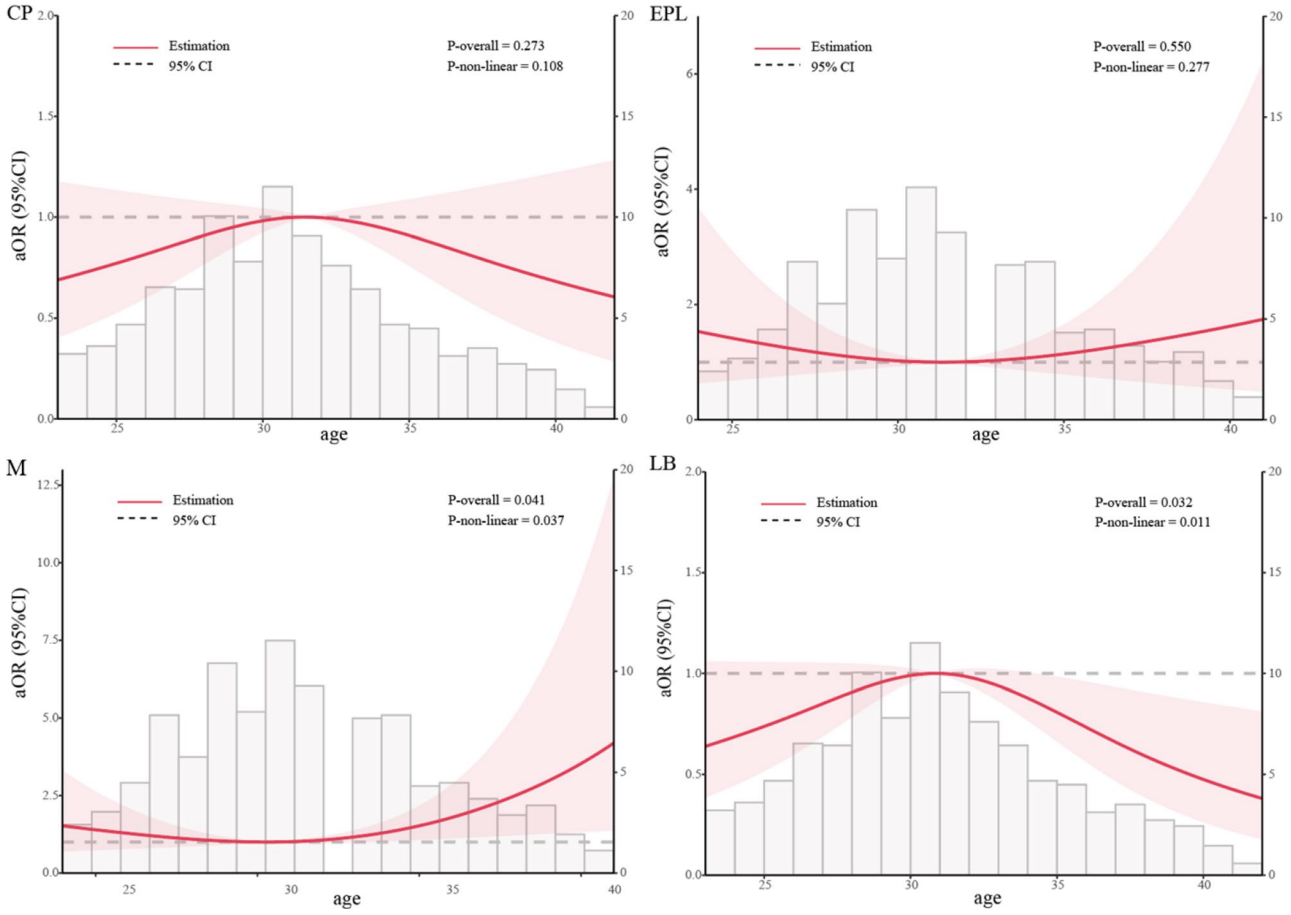

Fig. 2 Restricted cubic spline for turning point of age. CP, clinical pregnancy; EPL, early pregnancy loss; M, miscarriage; LB, live birth

prior studies may stem from variations in subject selection and the inconsistent adjustments for potential confounding factors. Our study mitigated this by focusing exclusively on cases involving single blastocyst transfer, which reduced heterogeneity among the cases. Furthermore, younger women undergoing PGT may have more complex infertility etiologies [16, 17]. For instance, those with a history of repeated implantation failure (RIF) and recurrent spontaneous abortion (RSA) may still face higher risks of adverse pregnancy outcomes, even after the transfer of euploid embryos [18]. It is essential to account for this variable when addressing confounding factors, otherwise, the genuine influence of age on pregnancy outcomes may be masked. Additionally, some studies suggested that the number of previous miscarriages was associated with adverse pregnancy outcomes after PGT-A [19, 20]. Our study considered these confounding factors, which, however, were not mentioned in other studies exploring the relationship between age and pregnancy outcomes following euploid embryo transfer. Our findings revealed that, prior to adjusting for confounders, advanced maternal age was associated with reduced live birth rate. However, after adjustment, the impact of advanced maternal age on increased miscarriage rate also became apparent.

The reduced live birth rate in our study is primarily attributed to the increased miscarriage rate, which may be linked to several potential factors associated with advanced maternal age. As women age, they experience a decline in basal metabolic rate and muscle mass, making them more vulnerable to metabolic dysregulation, which in turn exacerbates inflammatory states and disrupts blood coagulation, indirectly raising miscarriage risk [21–24]. Importantly, this risk is not confined to the first trimester but may persist throughout the entire pregnancy. Additionally, as pregnancy progresses, there is an increased susceptibility to pregnancy-related complications in advanced age women, including a higher prevalence of Gestational Diabetes Mellitus (GDM) and Pregnancy-Induced Hypertension (PIH) [25]. Moreover, maternal age is an independent risk factor for placenta previa, particularly in primiparous women over 40, further increasing miscarriage risk [26]. Considering these factors, it is crucial to recognize the unique risks faced by older pregnant women and to monitor their health status throughout pregnancy. Tailored medical plans should

be developed based on the specific needs of advanced maternal age, including lifestyle modifications, nutritional supplementation, regular prenatal check-ups, and medical interventions as needed, with the goal of improving live birth rates in this group.

In addition, advanced maternal age may cause alterations in the endometrium at the molecular, cellular, and histological levels, resulting in defective decidualization of endometrial stromal cells, impaired endometrial receptivity, and disruptions in the structure and cellular composition of the endometrium [27, 28]. These changes could further contribute to placental dysfunction. However, there is currently no evidence to directly link the negative impact of advanced maternal age on the endometrium with an increased risk of miscarriage, highlighting the need for further research in this area.

Blastocyst morphology served as a critical parameter in assessing embryonic vitality. The inner cell mass develops into fetal structures, while the trophectoderm forms the placental structures. Numerous studies have illustrated that higher-grade blastocysts have superior developmental potential. Consistent with these findings, our data confirmed that the importance of the morphology of euploid blastocysts for pregnancy outcomes [29]. Furthermore, our study found higher clinical pregnancy rate following the transfer of D5 blastocysts compared to D6 blastocysts [30]. This phenomenon may be attributed to prolonged in vitro culture, which can exacerbate gene expression aberrations, epigenetic modifications, and mitochondrial dysfunction, thereby further compromising embryonic viability [31].

Our study employed multivariate logistic regression to account for confounders such as RSA and RIF thereby minimizing their potential influence on pregnancy outcomes. However, it is important to acknowledge the inherent limitations of our retrospective design, which may introduce common biases associated with such studies. Moreover, the data used in this analysis were derived exclusively from a single center, raising concerns about the generalizability of our results. Additionally, the limited sample size precluded us from conducting a more granular stratified analysis of the patient population aged 38 years and older. Furthermore, since we did not track the specific causes of miscarriage, we were unable to conduct a more detailed analysis of the specific impact of age on miscarriage. These factors may limit the generalizability of our results and the ability to apply our findings to different populations and settings.

Conclusion

In conclusion, our research indicates that increasing maternal age is associated with both a higher number of aneuploid embryos and a potential increase in the risk of miscarriage following euploid embryo transfer, which may consequently reduce the live birth rate. Further research is needed to elucidate the reasons for age-related reproductive decline following euploid embryo transfer, with particular focus on endometrial receptivity, placental function, and the long-term effects of metabolic dysregulation.

Abbreviations

GEE	Generalized estimating equations
PGT-A	Preimplantation genetic testing for aneuploidy
ART	Assisted reproductive technology
FET	Frozen embryo transfer
SET	Single embryo transfer
GnRH	Gonadotropin-releasing hormone
E_2	Estradiol
ICSI	Intracytoplasmic sperm injection
PGT-SR	Preimplantation genetic testing for structural rearrangements
NGS	Next-generation sequencing
PGT-M	Preimplantation genetic testing for monogenic diseases
BMI	Body mass index
RIF	Repeated implantation failure
RSA	Recurrent spontaneous abortion
GDM	Gestational diabetes mellitus
PIH	Pregnancy-induced hypertension

Acknowledgements

We want to express our thanks to all patients and their partners, nurses, doctors, and other medical staff in the Reproductive Center of Women's Hospital of Nanjing Medical University for agreeing to participate in this study.

Author contributions

Jiang W, Zheng ZC and Ling XF contributed to the conception and design. Jiang W, Zheng ZC contributed to writing article. Yan N and Yao S contributed to the data collection and organization. Xie QJ and Ni DY contributed to reviewing the literature. Cao SR and Zhao C contributed to revising the manuscript. All authors participated in the analysis and interpretation of data in this article. All authors read and approved the final manuscript.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work is supported by National Natural Science Foundation of China (grant nos. 2021YFC2700601-1).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the approved guidelines and approved by the Ethics Committee of Nanjing Women and Children's Healthcare Hospital (2024KY-011). Informed patient consent was not required as the study was retrospective in nature and analyzed patient data anonymously. A statement from the Ethics Committee of Nanjing Maternity and Child Health Care Hospital waived the need for informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.
Clinical trial number: not applicable.

Author details

[1]Department of Reproductive Medicine, Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital, 123 Tianfeixiang, Mochou Road, Nanjing 210004, Jiangsu, China

[2]Department of Gynaecology, Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital, 123 Tianfeixiang, Mochou Road, Nanjing 210004, Jiangsu, China

Received: 14 September 2024 / Accepted: 16 January 2025
Published online: 06 February 2025

References

1. Beaujouan É, Reimondos A, Gray E, Evans A, Sobotka T. Declining realisation of reproductive intentions with age. Hum Reprod (Oxford England). 2019;34(10):1906–14.
2. Kearney AL, White KM. Examining the psychosocial determinants of women's decisions to delay childbearing. Hum Reprod (Oxford England). 2016;31(8):1776–87.
3. Kasaven LS, Saso S, Getreu N, O'Neill H, Bracewell-Milnes T, Shakir F et al. Age-related fertility decline: is there a role for elective ovarian tissue cryopreservation? Human reproduction (Oxford, England) 2022, 37(9):1970–9.
4. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ (Clinical Res ed). 2019;364:l869.
5. Mihalas BP, Pieper GH, Aboelenain M, Munro L, Srsen V, Currie CE, et al. Age-dependent loss of cohesion protection in human oocytes. Curr Biology: CB. 2024;34(1):117–e131115.
6. Gruhn JR, Zielinska AP, Shukla V, Blanshard R, Capalbo A, Cimadomo D, et al. Chromosome errors in human eggs shape natural fertility over reproductive life span. Sci (New York NY). 2019;365(6460):1466–9.
7. The use of. Preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril. 2018;109(3):429–36.
8. Neal SA, Morin SJ, Franasiak JM, Goodman LR, Juneau CR, Forman EJ, et al. Preimplantation genetic testing for aneuploidy is cost-effective, shortens treatment time, and reduces the risk of failed embryo transfer and clinical miscarriage. Fertil Steril. 2018;110(5):896–904.
9. Lawrenz B, Kalafat E, Ata B, Gallego RD, Melado L, Bayram A, et al. Ongoing pregnancy rates in single euploid frozen embryo transfers remain unaffected by female age: a retrospective study. Reprod Biomed Online. 2024;49(2):104074.
10. Cozzolino M, Capalbo A, Garcia-Velasco JA, Pellicer A, Vaiarelli A, Galliano D et al. In vitro fertilization and perinatal outcomes of patients with advanced maternal age after single frozen euploid embryo transfer: a propensity score-matched analysis of autologous and donor cycles. Fertility and sterility 2024.
11. Vitagliano A, Paffoni A, Viganò P. Does maternal age affect assisted reproduction technology success rates after euploid embryo transfer? A systematic review and meta-analysis. Fertil Steril. 2023;120(2):251–65.
12. Awadalla MS, Vestal NL, McGinnis LK, Ahmady A, Paulson RJ. Effect of age and morphology on sustained implantation rate after euploid blastocyst transfer. Reprod Biomed Online. 2021;43(3):395–403.
13. Medicine CAR. Expert consensus on human embryo morphological assessment: cleavage-stage embryos and blastocysts grading criteria. Chin J Reprod Contracept. 2022;42(12):1218–25.
14. Reig A, Franasiak J, Scott RT Jr., Seli E. The impact of age beyond ploidy: outcome data from 8175 euploid single embryo transfers. J Assist Reprod Genet. 2020;37(3):595–602.
15. Irani M, Zaninovic N, Rosenwaks Z, Xu K. Does maternal age at retrieval influence the implantation potential of euploid blastocysts? Am J Obstet Gynecol. 2019;220(4):e379371–7.
16. Yao Y, Ye Y, Chen J, Zhang M, Cai X, Zheng C. Maternal-fetal immunity and recurrent spontaneous abortion. American journal of reproductive immunology (New York, NY: 1989) 2024, 91(5):e13859.
17. Qian J, Zhang N, Lin J, Wang C, Pan X, Chen L, et al. Distinct pattern of Th17/Treg cells in pregnant women with a history of unexplained recurrent spontaneous abortion. Biosci Trends. 2018;12(2):157–67.
18. Liu X-Y, Fan Q, Wang J, Li R, Xu Y, Guo J, et al. Higher chromosomal abnormality rate in blastocysts from young patients with idiopathic recurrent pregnancy loss. Fertil Steril. 2020;113:853–64.
19. Ni T, Wu Q, Zhu Y, Jiang W, Zhang Q, Li Y, et al. Comprehensive analysis of the associations between previous pregnancy failures and blastocyst aneuploidy as well as pregnancy outcomes after PGT-A. J Assist Reprod Genet. 2020;37:579–88.
20. Zhao ST, Liu YB, Zhang Q, Ni TX, Yan JH. The impact of the number of previous miscarriages on embryo euploid rate and pregnancy outcomes in patients with unexplained recurrent pregnancy loss. Zhonghua Yi Xue Za Zhi 2023 Sep 26, 103(36):2874–80.
21. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB, et al. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. Diabetes Care. 2003;26(2):372–9.
22. Trohl J, Schindler M, Buske M, de Nivelle J, Toto Nienguesso A, Navarrete Santos A. Advanced maternal age leads to changes within the insulin/IGF system and lipid metabolism in the reproductive tract and preimplantation embryo: insights from the rabbit model. Mol Hum Reprod 2023, 29(12).
23. Zhu XZ, Deng ZM, Dai FF, Liu H, Cheng YX. The impact of early pregnancy metabolic disorders on pregnancy outcome and the specific mechanism. Eur J Med Res. 2023;28(1):197.
24. Azizi R, Soltani-Zangbar MS, Sheikhansari G, Pourmoghadam Z, Mehdizadeh A, Mahdipour M, et al. Metabolic syndrome mediates inflammatory and oxidative stress responses in patients with recurrent pregnancy loss. J Reprod Immunol. 2019;133:18–26.
25. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecology: Official J Int Soc Ultrasound Obstet Gynecol. 2013;42(6):634–43.
26. Li J, Yan J, Jiang W. The role of maternal age on adverse pregnancy outcomes among primiparous women with singleton birth: a retrospective cohort study in urban areas of China. J maternal-fetal Neonatal Medicine: Official J Eur Association Perinat Med Federation Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2023;36(2):2250894.
27. Pathare ADS, Loid M, Saare M, Gidlöf SB, Zamani Esteki M, Acharya G, et al. Endometrial receptivity in women of advanced age: an underrated factor in infertility. Hum Reprod Update. 2023;29(6):773–93.
28. Woods L, Dean W, Hemberger M, REPRODUCTIVE AGEING. Altered histone modification landscapes underpin defects in uterine stromal cell decidualization in aging females. Reproduction. 2024;168(3):e240171.
29. Zhang WY, Johal JK, Gardner RM, Bavan B, Milki AA. The impact of euploid blastocyst morphology and maternal age on pregnancy and neonatal outcomes in natural cycle frozen embryo transfers. J Assist Reprod Genet. 2022;39(3):647–54.
30. Abdala A, Elkhatib I, Bayram A, Arnanz A, El-Damen A, Melado L, et al. Day 5 vs day 6 single euploid blastocyst frozen embryo transfers: which variables do have an impact on the clinical pregnancy rates? J Assist Reprod Genet. 2022;39(2):379–88.
31. Tiosano D, Mears JA, Buchner DA. Mitochondrial dysfunction in primary ovarian insufficiency. Endocrinology. 2019;160(10):2353–66.

Publisher's note