

Differences in Pregnancy Outcomes Between in vitro Fertilization and Natural Conception in Nulliparous Singleton Pregnancies of Advanced Maternal Age: A Study Based on Propensity Score Matching and Cohort Retrospective Analysis

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Objective: To compare pregnancy outcomes between in vitro fertilization (IVF) and natural conception in singleton pregnancies among nulliparous of advanced maternal age.

Patients and methods: This retrospective analysis utilized propensity score matching (PSM) on 128 cases in the IVF group and 196 cases in the natural conception group, selected from the Second Nanning People's Hospital between January 2020 and December 2023. Early and late pregnancy outcomes assessed included hemoglobin (Hb) levels, oligohydramnios, fetal growth restriction (FGR), gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), placenta previa, placental abruption, premature rupture of membranes, fetal distress, mode of delivery, gestational age at delivery, preterm birth, low birth weight, macrosomia, and blood loss during delivery.

Results: The IVF group exhibited a higher incidence of oligohydramnios and a lower incidence of low birth weight compared to the natural conception group, with both differences being statistically significant ($P < 0.05$). No significant differences were found between the two groups for other pregnancy complications.

Conclusion: Pregnancy outcomes for IVF and natural conception are comparable in singleton pregnancies among nulliparous of advanced maternal age. However, clinicians should remain vigilant regarding the risks of oligohydramnios and low birth weight in IVF pregnancies to ensure appropriate monitoring and intervention.

Keywords: In Vitro Fertilization, (IVF), nulliparous of advanced maternal age, pregnancy outcomes

Introduction

In resource-rich countries, the median age of women giving birth for the first time has been progressively increasing, with many women starting families after turning 35.¹ This indicates a rising trend of advanced maternal age, reflecting the influence of social and economic factors. In recent years, driven by economic growth and evolving attitudes toward marriage, the number of first-time mothers in the advanced maternal age bracket has been rising annually in our country. Alongside the increased use of assisted reproductive technology, the incidence of in vitro fertilization (IVF) among older first-time mothers has also been steadily climbing. This emphasizes the growing proportion of older first-time mothers utilizing assisted reproductive technology. Globally, there has been a notable surge in the proportion of women

postponing childbirth until their late 30s and early 40s.² This trend is prevalent worldwide, further underscoring the relevance of the research. Currently, there is no universally accepted definition for “advanced maternal age” which generally refers to women in the later stages of their reproductive lifespan, typically aged 35 years or older.³ An advanced maternal age nulliparous woman is defined as one who gives birth to her first child at the age of 35 or above.⁴ Advanced maternal age is associated with increased risks of obstetric and perinatal complications, as well as a higher likelihood of pregnancy-related issues.^{3,5} This highlights the specific risks faced by older first-time mothers. An international meta-analysis has demonstrated that the risks of stillbirth, cesarean deliveries, and maternal mortality rise with advancing maternal age.⁶ A retrospective study conducted in our country has revealed a substantial increase in the prevalence of gestational hypertension, iron-deficiency anemia, and gestational diabetes mellitus among women of advanced maternal age.⁷ Furthermore, amid an aging population and a growing incidence of infertility, an increasing number of older women are turning to assisted reproductive technology to conceive. This trend underscores the importance of conducting comparative analyses of pregnancy outcomes between IVF and natural conception (NC) in first-time mothers of advanced maternal age. Currently, there are few studies specifically targeting nulliparous women of advanced maternal age, and existing research primarily covers the population of advanced maternal age pregnancies, including both nulliparous and multiparous women. Therefore, we conducted this study to provide some clinical guidance for the population of advanced maternal age who are infertile. By doing so, we aim to provide theoretical support for perinatal care among singletons conceived through IVF in nulliparous of advanced maternal age, assisting clinicians in more accurately assessing and managing the risks associated with advanced maternal age during pregnancy, ultimately enhancing maternal and infant outcomes.

Patients and Methods

Patients

Our study was conducted at a reproductive medicine center located in a city with 13 tertiary hospitals. Annually, our center performs approximately 3524 in vitro fertilization (IVF) cycles, with a pregnancy success rate of 48.03%. Among the successful pregnancies, around 79.75% are singleton pregnancies. The center also reports an annual delivery volume of approximately 3,530 cases, which includes a diverse population of young primiparous women, women of advanced maternal age (AMA), and women with multiple gestation.

To ensure the validity of our findings, we established strict inclusion criteria for patient enrollment. These criteria were designed to minimize selection bias and to focus on specific patient populations relevant to our research objectives. Only patients who met these criteria were included in the study, allowing us to draw meaningful conclusions from our data.

We selected nulliparous women with singleton pregnancies aged 35–44 years who delivered at Nanning Second People’s Hospital from January 2020 to December 2023 as the study subjects. The IVF group consisted of 128 cases, while the natural conception group included 196 cases.

Given the high volume of IVF cycles performed annually at our center, we are able to capture a diverse population of patients, including those with low-prevalence conditions. For instance, our inclusion criteria allowed us to identify cases of gestational diabetes mellitus and hypertensive disorders, are critical to understanding pregnancy outcomes in our study population.

Inclusion and Exclusion Criteria

Inclusion criteria: Age \geq 35 years; singleton pregnancy; nulliparous; regular prenatal check-ups; no severe comorbidities (severe comorbidities defined as conditions that may significantly impact maternal and fetal health during pregnancy, including but not limited to heart disease, severe anemia, hyperthyroidism, immune-related diseases, renal diseases, and any other serious conditions that may lead to pregnancy complications).

Exclusion criteria: Multiple pregnancies; multiparous women; fetal congenital anomalies; stillbirth prior to admission; incomplete clinical data.

Method

This study has received approval from the Ethics Committee of the Second Nanning People's Hospital. Ethics approval for the study was obtained from the Ethics Committee of the Second Nanning People's Hospital. This clinical study will adhere to the provisions of the Declaration of Helsinki, the Ethical Review Measures for Research Involving Human Life Sciences and Medical Research, the Administrative Measures for Investigator-Initiated Clinical Research in Medical and Health Institutions (Trial), and the Regulations on the Management of Human Genetic Resources of the People's Republic of China, as well as other relevant laws and regulations. The Ethics Committee of the Second Nanning People's Hospital has agreed to waive the requirement for informed consent from the participants.

The Ethics Committee has agreed to waive the requirement for informed consent from the participants, as the study involves minimal risk and does not compromise the rights and welfare of the participants.

The project researchers will collectively bear the responsibility for maintaining the confidentiality of the participants' relevant information and commit to not disclosing any content related to the participants. Any public report of the results of this study will not reveal the personal identities of the participants. We will make every effort, within the bounds of the law, to protect the privacy of the participants' personal medical data and personal information.

Methods and Observational Indicators

We divided the eligible pregnant women into IVF and natural conception groups, comparing the following outcomes during early pregnancy (before 13 weeks of gestation) with those during late pregnancy (the most recent assessment before admission for delivery): hemoglobin (HB) levels, oligohydramnios, fetal growth restriction (FGR), gestational diabetes mellitus (GDM), hypertensive disorders, placenta previa, placental abruption, premature rupture of membranes, fetal distress, mode of delivery (vaginal delivery or cesarean section), gestational age at delivery, preterm birth, low birth weight, macrosomia, and blood loss during delivery.

Statistical Analysis

The statistical analysis was conducted using SPSS 29.0 software (IBM Corp., Armonk, NY, USA) statistical software. Propensity Score Matching (PSM) was applied to match participants from the natural conception group based on maternal age, pre-pregnancy body mass index (BMI), parity, age at menarche, and hemoglobin (HB) levels during early pregnancy. A nearest neighbor matching method was used for a 1:1 pairing, with a matching tolerance set at 0.02. Prior to PSM, there were 128 cases in the IVF group and 196 cases in the natural conception group. Following PSM, a total of 228 mothers were included in the analysis, with 114 in the IVF group and 114 in the natural conception group. Normally distributed or approximately normally distributed continuous data were expressed as mean \pm standard deviation ($\bar{x} \pm s$), and comparisons between the two groups were performed using *t*-tests, with $P < 0.05$ indicating statistical significance. Categorical data were expressed as percentages (%), and comparisons were made using the χ^2 -test; when the expected count was < 5 , Fisher's exact test was used, with $P < 0.05$ indicating statistical significance.

Results

Differences in Demographic Characteristics Between the Two Groups

Prior to PSM, the age of the IVF group was higher than that of the natural conception group, and the difference was statistically significant ($P < 0.05$). There were no statistically significant differences in BMI, age at menarche, and parity ($P > 0.05$). Following PSM, there were no statistically significant differences in age, BMI, age at menarche, and parity between the two groups ($P > 0.05$) (Table 1).

Comparison of Hemoglobin Levels and Pregnancy Complications

Before matching, early pregnancy hemoglobin (HB) and gestational diabetes mellitus (GDM) levels were higher in the IVF group compared to the natural conception (NC) group, with statistically significant differences ($P < 0.05$). However, there were no statistically significant differences in late pregnancy HB, hypertensive disorders of pregnancy (HDP), placenta previa, and

Table 1 Comparison of General Data Between the Two Groups ($\bar{x} \pm s$), M(P25,P75)

| Group | Age (year) | BMI (kg/m ²) | Menarche(year) | Pregnancies |
|-----------------|------------|--------------------------|----------------|-------------|
| Pre-matching | | | | |
| IVF (128 cases) | 37(36,39) | 21.88(20.23,23.98) | 13(13,14) | 1.5(1,2) |
| NC (196 cases) | 36(35,38) | 21.27(20.30,24.74) | 13(12.25,13) | 2(1,3) |
| z | -3.375 | -1.018 | -1.617 | -0.743 |
| p | <0.001 | 0.308 | 0.106 | 0.457 |
| Post-matching | | | | |
| IVF (114 cases) | 37(36,38) | 22.35±2.99 | 13(13,14) | 2(1,3) |
| NC (114 cases) | 37(35,38) | 22.09±2.98 | 13(12,14) | 2(1,2) |
| t/z | -0.799 | 0.662 | -0.140 | -0.272 |
| p | 0.424 | 0.509 | 0.889 | 0.786 |

Abbreviations: BMI, Body Mass Index; IVF, in vitro fertilization; NC, natural conception.

placental abruption between the two groups ($P > 0.05$). Following PSM, there were no statistically significant differences in early and late pregnancy HB, GDM, HDP, placenta previa, and placental abruption between the two groups ($P > 0.05$) (Table 2).

Comparison of Pregnancy Outcomes

Before matching, the incidence of oligohydramnios and bleeding volume was higher in the IVF group compared to the natural conception (NC) group, with statistically significant differences ($P < 0.05$). However, there were no statistically significant differences in fetal growth restriction (FGR), macrosomia, low birth weight (LBW), preterm birth (PTB), premature rupture of membranes (PROM), fetal distress, postpartum hemorrhage (PPH), and mode of delivery ($P > 0.05$). Following PSM, the IVF group had a higher incidence of oligohydramnios compared to the NC group, while LBW was lower in the IVF group than in the NC group, with both differences being statistically significant ($P < 0.05$). There were no statistically significant differences in FGR, macrosomia, PTB, PROM, fetal distress, PPH, mode of delivery, and bleeding volume ($P > 0.05$) (Table 3).

Discussion

In this study, our primary objective was to compare pregnancy outcomes between in vitro fertilization (IVF) and natural conception (NC) among nulliparous of advanced maternal age. The results revealed that, although there were no statistically significant differences in the incidence of most pregnancy complications between the two groups, the IVF group exhibited a significantly higher rate of oligohydramnios compared to the NC group. Conversely, the incidence of low birth weight (LBW) was relatively lower in the IVF group. This finding suggests that, among nulliparous women of advanced maternal age, IVF may be associated with a higher risk of oligohydramnios but a decreased occurrence of LBW, which contrasts with some previous research findings. However, the underlying causes of oligohydramnios,

Table 2 Comparison of HB and Pregnancy Complications ($\bar{x} \pm s$), (N)%

| HB, Pregnancy Complications | Pre-matching | | | | Post-Matching | | | |
|-----------------------------|-----------------|----------------|-------------|-------|-----------------|----------------|-------------|-------|
| | IVF (128 cases) | NC (196 cases) | t/ χ^2 | p | IVF (114 cases) | NC (114 cases) | t/ χ^2 | p |
| HB(g/L) | | | | | | | | |
| 1 st trimester | 124.09±11.25 | 121.42±10.47 | 2.179 | 0.030 | 123.40±10.39 | 123.37±10.17 | 0.662 | 0.509 |
| 3 rd trimester | 120.52±11.58 | 119.45±12.98 | 0.750 | 0.454 | 120.11±11.23 | 120.42±13.93 | -0.183 | 0.855 |
| GDM | 51(39.84%) | 57(29.08%) | 4.133 | 0.042 | 42(35.09%) | 36(31.58%) | 0.702 | 0.402 |
| HDP | 21(16.40%) | 35(17.86%) | 0.114 | 0.736 | 20(17.54%) | 21(18.42%) | 0.030 | 0.863 |
| Placenta previa | 4(3.13%) | 4(2.04%) | 0.378 | 0.717 | 3(2.63%) | 1(0.88%) | 1.018 | >0.99 |
| Placental abruption | 0(0.00%) | 2(1.02%) | 1.314 | 0.521 | 0(0.00%) | 1(0.88%) | 1.004 | >0.99 |

Abbreviations: HB, Hemoglobin; GDM, Gestational Diabetes Mellitus.

Table 3 Comparison of Pregnancy Outcomes M(P25,P75), (N)%

| Indicators | Pre-Matching | | | | Post-Matching | | | |
|-------------------------|-----------------|----------------|------------|----------|-----------------|----------------|------------|----------|
| | IVF (128 cases) | NC (196 cases) | z/χ^2 | <i>p</i> | IVF (114 cases) | NC (114 cases) | z/χ^2 | <i>p</i> |
| Oligohydramnios | 25(19.53%) | 22(11.22) | 4.308 | 0.038 | 21(18.42%) | 10(8.77%) | 4.517 | 0.034 |
| FGR | 3(2.34%) | 11(5.61%) | 2.001 | 0.157 | 3(2.63%) | 7(6.14%) | 0.662 | 0.509 |
| Macrosomia | 2(1.56%) | 2(1.02%) | 0.187 | 0.649 | 1(0.88%) | 1(0.88%) | 2.182 | 0.823 |
| LBW | | | 5.388 | 0.065 | | | 6.779 | 0.032 |
| Not yet full-term | 0(0.00%) | 8(4.08%) | | | 0(0.00%) | 6(5.26%) | | |
| Full term | 3(2.34%) | 5(2.55%) | | | 3(2.63%) | 5(4.39%) | | |
| PTB | | | 6,116 | 0.109 | | | 2.182 | 0.823 |
| (28–31 ⁺⁶ W) | 0(0.00%) | 4(2.04%) | | | 0(0.00%) | 1(0.88%) | | |
| (32–33 ⁺⁶ W) | 0(0.00%) | 3(1.53%) | | | 0(0.00%) | 1(0.88%) | | |
| (34–36 ⁺⁶ W) | 12(9.38%) | 11(5.61%) | | | 12(10.53%) | 10(8.77%) | | |
| PROM | | | 2.771 | 0.250 | | | 2.040 | 0.361 |
| Not yet full-term | 9(7.03%) | 6(3.06%) | | | 9(7.89%) | 4(3.51%) | | |
| Full term | 19(14.84%) | 31(15.82%) | | | 19(16.67%) | 20(17.54%) | | |
| Fetal distress | 12(9.38%) | 16(8.16%) | 0.144 | 0.704 | 9(7.89%) | 8(7.02%) | 0.064 | 0.801 |
| PPH | 5(3.91%) | 3(1.53%) | 1.851 | 0.272 | 3(2.63%) | 3(2.63%) | 0.00 | >0.99 |
| Delivery method | | | 4.095 | 0.129 | | | 1.616 | 0.446 |
| VD | 28(21.88%) | 62(31.63%) | | | 26(22.81%) | 31(27.19%) | | |
| CS | | | | | | | | |
| ICS | 51(39.84%) | 74(37.76%) | | | 45(39.47%) | 36(31.58%) | | |
| UCS | 49(38.28%) | 60(30.61%) | | | 43(37.72%) | 47(41.23%) | | |
| tive blood loss (mL) | 300(300,400) | 300(200,400) | −3.22 | 0.001 | 300(300,400) | 300(200,400) | −1.277 | 0.202 |

Abbreviations: FGR, Fetal growth restriction; LBW, Low birth weight; PTB, Preterm birth; PROM, Premature rupture of membranes; PPH, postpartum hemorrhage; VD, Vaginal Delivery; CS, Cesarean section; ICS, indicated cesarean section; NCS, No Indication Cesarean Section.

including potential comorbidities, were not investigated in our study, highlighting a significant limitation. It is important to emphasize that, despite the significant advancements in IVF technology that have expanded reproductive options for older women, clinical practice must remain vigilant regarding these potential risk factors. This underscores the need for rigorous monitoring and timely intervention during both early and late pregnancy for nulliparous of advanced maternal age. Furthermore, our study employed the propensity score matching (PSM) method to effectively control for confounding factors such as age, thereby enhancing the reliability of our findings. In light of these observations, we aim to avoid assumptions in our interpretations and focus on presenting our findings objectively. Future research endeavors should explore additional factors that influence pregnancy outcomes among nulliparous women of advanced maternal age, with the aim of refining and optimizing pregnancy management strategies.

Comparison of Hemoglobin Levels and Pregnancy Complications

In this study, we investigated the disparities in pregnancy outcomes between in vitro fertilization (IVF) and natural conception (NC) among nulliparous of advanced maternal age, with a specific emphasis on hemoglobin (Hb) levels during pregnancy and the occurrence of pregnancy complications. Prior to propensity score matching (PSM), our results revealed significantly higher early pregnancy Hb levels and a greater incidence of gestational diabetes mellitus (GDM) in the IVF group compared to the NC group ($P < 0.05$). However, no statistically significant differences were observed in Hb levels, hypertensive disorders of pregnancy (HDP), placenta previa, or placental abruption during late pregnancy ($P > 0.05$). Following PSM, the differences in early and late pregnancy Hb levels, GDM, HDP, placenta previa, and placental abruption between the two groups were no longer significant ($P > 0.05$). These findings suggest that, among nulliparous of advanced maternal age, the pregnancy outcomes of IVF and NC tend to converge to a certain degree.

The risks of pregnancy complications are notably elevated in older mothers, particularly for conditions such as GDM and preeclampsia.⁸ Research has demonstrated that the incidence of gestational diabetes increases with age, with women aged 40 and older exhibiting a 3–6 times higher incidence compared to those aged 20–29.^{9,10} Furthermore, the likelihood

of a chronic hypertension diagnosis among pregnant women aged 35 and older is 2–4 times higher than that of women aged 30–34.¹¹ Our observation of elevated early pregnancy Hb levels in the IVF group aligns with this, indicating that nulliparous of advanced maternal age may face a greater metabolic burden during early pregnancy. However, after accounting for other potential influencing factors through PSM, no significant differences in early pregnancy Hb levels or pregnancy complications were observed between the IVF and NC groups. This suggests that, while nulliparous of advanced maternal age may initially exhibit a higher metabolic burden, this burden becomes comparable when other factors are considered.

Moreover, the risks of placenta previa and placental abruption are closely associated with advanced maternal age.¹² Studies have shown that women aged 40 and older have a tenfold increased risk of placenta previa compared to those aged 20–29, despite the absolute risk being relatively low (0.25% vs 0.03%).¹³ Consistent with our findings, no significant differences in these complications were observed between the IVF and NC groups, indicating that the overall pregnancy risks for nulliparous of advanced maternal age are primarily driven by age itself rather than solely by the mode of conception.

Furthermore, women undergoing assisted reproductive technology (ART) face a nearly 50% increased risk of hypertensive disorders during pregnancy,¹⁴ highlighting the importance of meticulous attention to the management of pregnancies in advanced maternal age. Although our study did not significantly differentiate between IVF and NC in terms of pregnancy complications among nulliparous of advanced maternal age, the impact of age on pregnancy risk is evident. Therefore, comprehensive assessment and monitoring of the nulliparous of advanced maternal age are crucial in clinical management.

Comparison of Pregnancy Outcomes

In this study, we conducted a comprehensive analysis of various indicators associated with pregnancy outcomes. The results revealed that the IVF group had significantly higher rates of oligohydramnios and blood loss compared to the NC (natural conception) group ($P < 0.05$). This finding may reflect the specific risks linked to IVF pregnancies, particularly concerning amniotic fluid management and blood loss control. While the IVF group demonstrated significant differences in oligohydramnios, no statistically significant differences were observed in other indicators, including fetal growth restriction (FGR), macrosomia, low birth weight (LBW), preterm birth (PTB), premature rupture of membranes (PROM), fetal distress, postpartum hemorrhage (PPH), mode of delivery, and other measures of blood loss ($P > 0.05$).

Notably, the high rate of elective cesarean sections in the IVF group warrants attention. Literature indicates an increasing prevalence of cesarean requests among pregnant women, particularly those of advanced maternal age.¹⁵ Studies consistently show that women aged ≥ 35 are more likely to experience dystocia¹⁶ and to undergo cesarean delivery.^{10,11,17} This suggests that older mothers may face an elevated risk of cesarean delivery, potentially due to age-related physiological changes and complications. Regarding low birth weight, research indicates that infants with fathers aged >45 have a significantly increased risk of LBW, PTB, and very preterm birth.¹⁸ The educational level of both parents significantly influences birth weight, with parents having more than 12 years of education associated with a reduced risk of term LBW and macrosomia.¹⁹ Interestingly, the IVF group exhibited a lower rate of LBW compared to the NC group, which contrasts with previous studies that reported higher risks of PTB and LBW in IVF singleton pregnancies compared to natural conception.^{20–22} This discrepancy may be attributed to the age of the maternal partner and the education levels of both partners; however, we did not collect data on these variables. This limitation highlights the need for future studies to include comprehensive data on maternal health conditions to better understand the risk factors associated with oligohydramnios and other pregnancy complications in this population.

While IVF pregnancies present higher risks in certain aspects, they do not significantly exceed those of natural conception in other indicators. This underscores the need for clinical management to comprehensively consider age, mode of conception, and other socioeconomic factors to optimize pregnancy outcomes for older mothers. Additionally, advanced maternal age increases the risk of pregnancy complications, including congenital anomalies and cesarean delivery,⁵ which requires attention in clinical practice. Therefore, management strategies for older mothers should be meticulously designed to reduce the rates of cesarean sections and associated complications. This study underscores the importance of monitoring and identifying potential comorbidities that could contribute to pregnancy complications such as oligohydramnios, particularly in nulliparous women of advanced maternal age undergoing IVF. Future studies should aim to include comprehensive data on maternal health conditions to better understand these risks.

Limitations

This study is a retrospective analysis focused solely on patients undergoing in vitro fertilization (IVF). Unfortunately, we did not differentiate between fresh and frozen embryo transfers in our data collection. This limitation restricts our ability to provide insights into how the incidence of certain diseases may vary between these two approaches. Future studies should consider examining these distinctions to enhance our understanding of the relationship between comorbidities and IVF outcomes.

Conclusions

In conclusion, there appear to be no significant differences in pregnancy complications and outcomes between nulliparous of advanced maternal age undergoing in vitro fertilization (IVF) and those conceiving naturally (NC). This finding offers theoretical support and reassurance to older women facing infertility who are considering IVF. However, attention must be paid to the risks of oligohydramnios and low birth weight. Future research should continue to explore strategies for monitoring pregnancies among nulliparous of advanced maternal age, as well as conduct in-depth analyses of the age and educational level of their partners. Such endeavors are crucial for optimizing intervention measures aimed at maximizing maternal and neonatal outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors have no conflicts of interest to declare for this work.

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