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ORIGINAL RESEARCH

Pregnancy Outcomes Following Assisted Reproductive Technology in Advanced Maternal Age Primiparous Women: A Retrospective Cohort Study

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Purpose: To evaluate maternal and neonatal outcomes following assisted reproductive technology (ART) in advanced maternal age (AMA) primiparous women.

Patients and Methods: This retrospective cohort study analyzed 2329 AMA primiparous women (≥35 years) who delivered singleton pregnancies at Northwest Women's and Children's Hospital between January 2016 and January 2020. Participants were stratified into ART (n=422) and spontaneous conception (SC, n=1907) groups. Maternal characteristics, obstetric complications, and neonatal outcomes were compared using multivariate logistic regression to adjust for confounders.

Results: ART patients exhibited significantly higher maternal age (37.48 ± 2.44 vs 36.65 ± 1.90 years, *p* < 0.001) and BMI (27.79 ± 3.34 vs 27.61 ± 8.12 kg/m², *p* = 0.016). ART was independently associated with increased risks of preeclampsia (adjusted odds ratio [aOR] 1.89, 95% confidence interval [CI] 1.25–2.86), cesarean delivery (aOR 2.31, 95% CI 1.74–3.06), preterm birth (aOR 1.55, 95% CI 1.10–2.19), and neonatal intensive care unit (NICU) admission (aOR 2.38, 95% CI 1.68–3.37). Conversely, SC pregnancies showed higher rates of preterm premature rupture of membranes (PPROM; 26.43% vs 17.30%, *p* < 0.001). No significant differences were observed in gestational diabetes mellitus (33.18% vs 31.31%, *p* = 0.455) or placental abruption (0.95% vs 1.42%, *p* = 0.313).

Conclusion: In AMA primiparas, ART selectively elevates risks of preeclampsia and neonatal morbidity, necessitating targeted antenatal surveillance. These findings underscore the importance of preconception counseling and individualized management for this growing patient population.

Keywords: advanced maternal age, assisted reproductive technology, primiparity, perinatal outcomes, neonatal outcomes

Advanced maternal age (AMA), typically defined as maternal age ≥35 years at delivery, has become a global public health concern with significant demographic shifts observed in both developed and developing nations.[1] In China, the average age of first pregnancy has increased by 1.65 years between 2013–2019, reflecting an annual delay of 0.3 years.[2] This trend is driven by complex socioeconomic factors, including rising costs of living, educational attainment, career prioritization, and declining fertility intentions.[3] Concurrently, ART has emerged as a critical intervention, with over 10 million children born through ART procedures worldwide since 1987.[4] However, the intersection of AMA and ART presents unique clinical challenges that warrant rigorous investigation.

While ART enables pregnancy achievement in older women, its impact on perinatal outcomes remains controversial. Existing evidence underscores AMA as an independent risk factor for adverse maternal outcomes including gestational hypertension, preeclampsia, and gestational diabetes mellitus.[5] Neonatal risks are equally pronounced, with meta-analyses demonstrating elevated rates of preterm birth and low birth weight in AMA pregnancies.[6] These risks may be compounded by ART, which has been associated with placental dysfunction through mechanisms such as impaired trophoblast invasion and

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epigenetic modifications.[7] Notably, For AMA women, IVF-ET pregnancy may lead to a higher incidence of pregnancy complications and adverse delivery outcomes, but this might be due to an increased rate of multiple pregnancies.[8]

Some studies report that ART does not independently increase risks when controlling for age,[9] whereas others demonstrate higher rates of placental-mediated complications in ART pregnancies.[10] These discrepancies may stem from heterogeneous study populations, with most evidence derived from mixed-age cohorts or multifetal pregnancies.

Notably, primiparous AMA women represent a distinct high-risk subgroup. Primiparity compounds age-related risks due to nulliparous uterine vascular adaptation,[5] yet limited data exist focusing exclusively on this population. Existing studies either combine multiparous women[11] or lack adjustment for critical confounders like parity.[12] This knowledge gap impedes evidence-based counseling for the growing cohort of AMA primiparas opting for ART.

To address these limitations, we conducted this retrospective cohort study comparing 2329 AMA primiparous women with singleton pregnancies, rigorously controlling for maternal age and parity. Our study aims to: Quantify the independent effect of ART on maternal and neonatal outcomes in AMA primiparas; Identify risk profiles specific to this population to guide clinical management.

Patients and Methods

Study Design and Population

This retrospective cohort study was conducted at Northwest Women's and Children's Hospital, a tertiary care center in Xi'an, China. We analyzed data from 2329 primiparous women aged ≥35 years who delivered singleton live births between January 1, 2016, and January 1, 2020. Participants were stratified into two groups based on conception method: the ART group (n=422) comprising women who underwent in vitro fertilization and embryo transfer (IVF-ET), and the spontaneous conception (SC) group (n=1907).

Inclusion and Exclusion Criteria

Inclusion criteria: Primiparous women aged ≥35 years at delivery. Singleton pregnancy ≥28 weeks gestation. Complete medical records available. For ART group: only IVF-ET cycles included (excluding cases with fetal reduction). Exclusion criteria: (1) Pre-pregnancy comorbidities of serious medical conditions (cardiovascular, hepatic, renal, or immune system diseases); (2) Multifetal pregnancies or incomplete clinical data. The general maternal conditions, maternal outcomes and infant outcomes of the two groups were retrospectively analysed. This retrospective study utilized anonymized clinical data extracted from electronic medical records. The Ethics Committee of Northwest Women's and Children's Hospital waived the requirement for individual informed consent as the research involved no more than minimal risk to participants and used pre-existing de-identified data (Approval No. 2022-049). This study complies with the Declaration of Helsinki.

Diagnostic Criteria

All diagnoses were made according to the 9th edition of Chinese "Obstetrics and Gynecology".[13] Comparing the following outcomes in two groups: hypertensive disorders of pregnancy, pre-eclampsia, gestational diabetes mellitus, diabetes mellitus combined with pregnancy, anaemia, placental abruption, premature rupture of membranes, intrahepatic cholestasis in pregnancy, post-partum haemorrhage, stillbirths, foetal distress, low birth weight babies, macrosomic babies and preterm births.

Statistical Analysis

Data analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) and compared using Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Categorical variables were expressed as frequencies (%) and analyzed using the chi-square test or Fisher's exact test. Multivariate logistic regression was performed to adjust for maternal age, BMI, and parity. Variables with $p<0.1$ in univariate analysis were included in the final model. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated to determine independent associations. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The ART group demonstrated significantly higher maternal age (37.48±2.44 years vs 36.65±1.90 years, p<0.001) and BMI (27.79±3.34 kg/m² vs 27.61±8.12 kg/m², p=0.016) compared to the spontaneous conception (SC) group. The proportion of women aged ≥40 years was markedly higher in the ART group (22.04% vs 8.65%, p<0.001). Gestational age at delivery was significantly shorter in ART pregnancies (38.49±1.95 weeks vs 38.97±1.71 weeks, p<0.001), while neonatal birth weights showed no statistical difference between groups (3224.45±575.56g vs 3275.90±513.07g, p=0.312) (Table 1).

Maternal Outcomes

The ART group exhibited significantly higher rates of: Preeclampsia (9.24% vs 5.14%, χ^2=10.51, p=0.001), Cesarean delivery (80.09% vs 63.08%, χ^2=44.67, p<0.001); Conversely, the SC group demonstrated higher incidence of: Preterm premature rupture of membranes (PPROM) (26.43% vs 17.30%, χ^2=15.46, p<0.001), No significant differences were observed in: Gestational hypertension (11.61% vs 9.28%, p=0.143), Gestational diabetes mellitus (33.18% vs 31.31%, p=0.455), Placental abruption (0.95% vs 1.42%, p=0.313) Postpartum hemorrhage (1.42% vs 2.36%, p=0.234) (Table 2).

Neonatal Outcome

ART-conceived neonates showed significantly higher rates of: Low birth weight (9.24% vs 6.14%, χ^2=5.34, p=0.021), Preterm birth (11.85% vs 8.02%, χ^2=6.36, p=0.012), NICU admission (13.27% vs 6.08%, χ^2=26.13, p<0.001), No significant differences were found in: Stillbirth (0% vs 0.26%, p=0.368), Fetal distress (3.08% vs 2.99%, p=0.921), Macrosomia (6.16% vs 6.03%, p=0.919), Neonatal malformations (1.18% vs 0.89%, p=0.367). Key findings are summarized in Tables 1 and 2, presenting both unadjusted and adjusted analyses for comprehensive assessment of outcomes (Table 2).

To control for potential confounders including maternal age, BMI, and parity, we performed multivariate logistic regression analysis (Table 3). ART remained independently associated with:

- Preeclampsia (adjusted odds ratio [aOR] 1.89, 95% confidence interval [CI] 1.25–2.86)
- Cesarean delivery (aOR 2.31, 95% CI 1.74–3.06)
- Preterm birth (aOR 1.55, 95% CI 1.10–2.19)
- NICU admission (aOR 2.38, 95% CI 1.68–3.37)

No significant associations were found between ART and gestational diabetes mellitus (aOR 1.12, 95% CI 0.89–1.41), placental abruption (aOR 0.67, 95% CI 0.23–1.95), or postpartum hemorrhage (aOR 0.60, 95% CI 0.26–1.39).

Discussion

This large retrospective cohort study of 2329 advanced maternal age (AMA) primiparous women demonstrated that ART-conceived pregnancies were independently associated with increased risks of preeclampsia (aOR 1.89), cesarean delivery (aOR 2.31), preterm birth (aOR 1.55), and NICU admission (aOR 2.38) compared to spontaneous conceptions, even after

Table 1 Comparison of Baseline Characteristics Between ART and Spontaneous Conception (SC) Groups

Characteristic	ART Group (n=422)	SC Group (n=1907)	Statistical Test	p-value
Maternal Age (years)	37.48 ± 2.44	36.65 ± 1.90	U = −6.304	<0.001
BMI (kg/m²)	27.79 ± 3.34	27.61 ± 8.12	U = −2.417	0.016
Gestational Age at Delivery (weeks)	38.49 ± 1.95	38.97 ± 1.71	U = −5.486	<0.001
Birthweight (g)	3224.45±75.56	3275.90±13.07	U = −1.012	0.312
Women ≥40 years, n (%)	93 (22.04%)	165 (8.65%)	χ^2 = 62.85	<0.001

Notes: Continuous variables presented as mean ± standard deviation (SD); categorical variables as n (%). *U*: Mann–Whitney *U*-test statistic for non-parametric data; χ^2: chi-square test for proportions. Bolded *p*-values indicate statistical significance (<0.05).
Abbreviations: ART, assisted reproductive technology; BMI, body mass index; SC, spontaneous conception.

Table 2 Comparison of Pregnancy Complications and Neonatal Outcome Between the Two Groups [n (%)]

Characteristic	ART Group (n=422)	SC Group (n=1907)	X^2	*P*-value
Maternal outcomes				
Cesarean section	338 (80.09)	1203 (63.08)	44.67	<0.001
HDP	49 (11.61)	177 (9.28)	2.14	0.143
Preeclampsia	39 (9.24)	98 (5.14)	10.51	0.001
GDM	140 (33.18)	597 (31.31)	0.56	0.455
PGDM	12 (2.84)	49 (2.57)	0.10	0.750
Anemia	157 (37.2)	705 (36.97)	0.01	0.928
Placental abruption	4 (0.95)	27 (1.42)	0.64	0.313
PROM	73 (17.3)	504 (26.43)	15.46	<0.001
ICP	6 (1.42)	19 (1)	0.59	0.443
PPH	6 (1.42)	645 (2.36)	1.42	0.234
Neonatal outcomes				
Stillbirth	0 (0)	5 (0.26)	0.59	0.368
Fetal distress	13 (3.08)	57 (2.99)	0.01	0.921
Low Apgar score	8 (1.9)	27 (1.42)	0.52	0.471
Neonatal structural anomaly	5 (1.18)	17 (0.89)	0.58	0.367
Low birth weight	39 (9.24)	117 (6.14)	5.34	0.021
Macrosomia	26 (6.16)	115 (6.03)	0.01	0.919
Preterm birth	50 (11.85)	153 (8.02)	0.64	0.012
NICU admission	56 (13.27)	116 (6.08)	26.13	<0.001

Abbreviations: HDP, hypertensive disorders of pregnancy; GDM, gestational diabetes mellitus; PGDM, pregestational diabetes mellitus; PROM, premature rupture of membranes; ICP, intrahepatic cholestasis of pregnancy; PPH, postpartum hemorrhage.

Table 3 Multivariate Logistic Regression Analysis of ART-Associated Outcomes (Adjusted for Maternal Age and BMI)

Outcome	aOR	95% CI	p-value
Preeclampsia	1.89	1.25–2.86	0.002
Cesarean delivery	2.31	1.74–3.06	<0.001
Preterm birth	1.55	1.10–2.19	0.012
NICU admission	2.38	1.68–3.37	<0.001
Gestational diabetes	1.12	0.89–1.41	0.332
Placental abruption	0.67	0.23–1.95	0.461

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

adjusting for maternal age and BMI. These findings align with existing evidence highlighting the interplay between ART and placental dysfunction,[10] while also revealing unique insights specific to AMA primiparas—a population that has been understudied in prior research.[8,14]

Characteristics of Pregnancy Risks for AMA Primiparous Women

AMA primiparous births are now becoming more common, with an increase in the age of first-time births possibly associated with women marrying later,[15] and anxiety during pregnancy and negative overall experiences of labour are more common among older first-time parents.[16] Older women have a higher risk of delivering preterm and low birth weight babies, which have long term negative effects on both the child and the mother.[17] The present study, after excluding twin births and repeat pregnancies in advanced maternal age, showed that the mean age (37.48 years) and the percentage of ultra-advanced age (≥40 years) was significantly higher in the ART group (22.04%), which is in line with the findings of another

study of ultra-AMA and these differences may be related to defective placenta function in pregnant women on ART.[14] Placental hypofunction due to advanced age may explain the shorter gestational weeks of delivery in the ART group (38.49 weeks vs 38.97 weeks, p<0.001). Of note, despite a higher BMI in the ART group (27.79 kg/m2 vs 27.61 kg/m2), there was no significant difference in the incidence of gestational diabetes mellitus (33.18% vs 31.31%, P=0.455), suggesting that age, rather than ART per se, may be the main cause of metabolic disturbances.

Selective Risks of ART

ART has been widely used in elderly primigravid women, in this study, the percentage of super-elderly primigravid women with ART pregnancies reached 22%, while the percentage of super-elderly primigravid women with natural pregnancies was only 8.65%, which indicates that the percentage of super-elderly primigravid women opting for ART pregnancies is more significantly higher, which is in line with the conclusions of other studies.[18,19] Some studies have concluded that assisted reproductive pregnancies do not appear to increase the risk of complications during pregnancy and perinatal outcomes in advanced maternal age,[20] while others have concluded the opposite,[21,22] that women with ART pregnancies have a higher cesarean section rate, obstetrical complications, and the risk of adverse fetal outcomes relative to spontaneous conception among women of advanced maternal age, but that these risks may be associated with an increase in the rate of twin pregnancies,[8] the cesarean section rate in the ART group in this study was 80.09% vs 63.08%, which, in addition to the factor of advanced age, may be related to the excessive intervention of doctors and patients on the "precious child", and we need to be vigilant about the long-term complications associated with non-medically indicated cesarean section.

In this study, after excluding the influence of multiple pregnancy factors, we found that among perinatal complications, only the incidence of premature rupture of membranes was significantly different between the two groups, and the pregnant women with natural pregnancy were significantly higher than those in the ART group (26.43% vs 17.30%), while no significant differences were observed in other aspects, which may be related to the higher average age of ART pregnant women and more medical treatment received before pregnancy, both the Pregnant women and doctors psychologically attached more importance to the outcome of this pregnancy and more often chose elective caesarean section delivery rather than waiting for spontaneous labour.

The incidence of perinatal complications such as hypertensive disorders of pregnancy and gestational diabetes mellitus in the present study did not differ between the two groups, which is in line with the findings of other studies.[8,23] The significantly elevated risk of preeclampsia in ART pregnancies (aOR 1.89, 95% CI 1.25–2.86) aligns with current understanding of ART-associated placental dysfunction,[10] the potential mechanisms may explain this association: Corpus luteum deficiency: Most ART cycles in our cohort used GnRH agonist protocols, which are known to suppress endogenous luteal function, potentially limiting production of vasoactive relaxin crucial for maternal cardiovascular adaptation.[24] Trophoblast invasion impairment: The supraphysiological hormonal environment during ovarian stimulation may disrupt normal trophoblast invasion and spiral artery remodeling.[25] Epigenetic modifications: In vitro culture conditions could induce epigenetic changes affecting placental development.[8]

Neonatal Outcomes: Reconciling Controversies

While ART-conceived neonates had higher rates of preterm birth and NICU admission, other outcomes (eg, stillbirth, fetal distress, macrosomia) showed no significant differences compared to SC neonates. This selective risk profile aligns with recent studies suggesting that ART primarily impacts fetal growth restriction and prematurity rather than congenital anomalies.[12,26,27] However, the twofold increase in NICU admissions highlights the need for enhanced postnatal surveillance in this population.[28]

Research Strengths and Limitations

The strengths of this study are: (1) focusing on singleton pregnancy and excluding the confounding factors of multiple pregnancies; (2) large sample size (n=2329), more representative data; (3) the first systematic analysis of elderly primigravid women in Northwest China. However, the study has the following limitations: (1) it did not differentiate between fresh and frozen-thawed embryo transfer cycles, which may have different effects on pregnancy outcomes; (2)

Absence of placental pathology data to explore preeclampsia mechanisms; and (3) the retrospective design may introduce selection bias. Future multicentre prospective studies combining placental pathology and long-term follow-up data in children are needed to further validate the findings.

Conclusion

In conclusion, our findings substantiate that ART in AMA primiparas confers selective perinatal risks requiring tailored clinical pathways. These results should inform international guidelines while highlighting the need for continued research into optimizing outcomes for this growing patient population.

Author Contributions

All authors made significant contributions to conception, study design, data acquisition, analysis, and interpretation; participated in drafting or critically revising the article; approved the final version; agreed on the target journal; and take responsibility for all aspects of the work.

Disclosure

All authors report no conflicts of interest in this work.

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