

Original Research

Assisted Reproductive Technology and Perinatal Outcomes: A Retrospective Cohort Study Stratified by Singleton and Multiple Pregnancies

Hyen Chul Jo^{1,2,3,†}, Juseok Yang^{1,2,3,†} , Jong Chul Baek^{1,2,3}, Ji Eun Park^{1,2,3,*} ¹Department of Obstetrics and Gynecology, Gyeongsang National University Changwon Hospital, 51427 Changwon, Republic of Korea²Department of Obstetrics and Gynecology, Gyeongsang National University School of Medicine, 52727 Jinju, Republic of Korea³Institute of Health Science, Gyeongsang National University, 52828 Jinju, Republic of Korea*Correspondence: ji1104@hanmail.net (Ji Eun Park)

†These authors contributed equally.

Academic Editor: Michael H. Dahan

Submitted: 1 August 2025 Revised: 15 September 2025 Accepted: 22 September 2025 Published: 27 November 2025

Abstract

Background: The global rise in pregnancies following assisted reproductive technology (ART) use has prompted ongoing evaluations into the impact of this technology on maternal and neonatal outcomes. Thus, this study aimed to compare outcomes between ART-conceived pregnancies and spontaneously conceived pregnancies, stratified by singleton and multiple pregnancies. **Methods:** We conducted a single-center retrospective cohort study at Gyeongsang National University Changwon Hospital in South Korea, using the medical records of women who delivered between January 2023 and December 2024. A total of 921 pregnancies were included, comprising 816 singleton pregnancies and 105 multiple pregnancies. Maternal and neonatal baseline characteristics were compared between ART-mediated and spontaneous conceptions within each gestational category. Outcomes assessed included postpartum hemorrhage (PPH), preterm birth (PTB), small for gestational age (SGA), neonatal intensive care unit (NICU) admission, 5-minute Apgar score < 7, and neonatal death. Multivariable logistic regression was performed to estimate adjusted odds ratios (aORs), controlling for relevant confounders. **Results:** Most maternal and neonatal outcomes did not significantly differ between ART-mediated and spontaneous conceptions in either singleton or multiple pregnancies. There were no statistically significant differences in the rates of PTB, SGA, NICU admission, low 5-minute Apgar score, and neonatal death between the groups. However, there was a significantly higher incidence of PPH in ART-conceived singleton pregnancies (25.7% vs. 9.4%), which remained significant in the multivariable analysis (aOR: 3.64, 95% confidence interval (CI): 2.21–5.98; $p < 0.001$). No significant difference in PPH incidence was observed in the multiple pregnancy cohort. **Conclusions:** Overall, most outcomes were comparable between ART-mediated and spontaneous conceptions. However, ART-conceived singleton pregnancies showed a significantly higher risk of PPH, even after adjusting for confounders. These findings underscore the need for heightened surveillance for PPH in ART-mediated singleton pregnancies, even in the absence of other risk factors.

Keywords: assisted reproductive technology; postpartum hemorrhage; perinatal outcomes; singleton pregnancy; multiple pregnancy; small for gestational age

1. Introduction

Since the birth of the first *in vitro* fertilization (IVF) baby in 1978, the global use of assisted reproductive technology (ART) has grown substantially, with an estimated 13 million ART-conceived children born worldwide to date [1]. Currently, approximately one ART-conceived infant is born every 35 seconds, and ART births account for around 5–10% of all deliveries in some high-income countries [1]. This rapid growth has firmly established ART as a mainstream clinical tool for women and families requiring reproductive assistance. Given the increasing prevalence of ART, concerns have emerged about its safety, particularly the impact on maternal and neonatal health.

Various studies have linked ART-conceived pregnancies to increased risks of adverse perinatal and neonatal outcomes, including preterm birth (PTB), low birth weight or small for gestational age (SGA), cesarean delivery, post-

partum hemorrhage (PPH), and hypertensive disorders [2–4]. However, some studies have found no significant differences in key perinatal outcomes between pregnancies conceived through ART and those conceived naturally [5,6]. These conflicting findings likely reflect heterogeneity in study design, populations, and analytic approaches. Some studies focused exclusively on singletons [3,7], whereas others included multiples without proper adjustment. Differences in controlling for maternal characteristics [2,4], stratifying by plurality [2,4,8], and defining outcomes [3,7] may have contributed to inconsistent results. These discrepancies raise questions about whether the observed risks are intrinsic to ART procedures, stem from underlying maternal characteristics, or are largely due to the higher incidence of multifetal gestation associated with ART [7,8].

For evidence-based clinical counseling and management, it is necessary to clarify whether ART independently



contributes to adverse perinatal and neonatal outcomes. To address this issue, we conducted a retrospective cohort analysis at a single institution to evaluate the impact of ART on perinatal and neonatal outcomes, including PTB, neonatal intensive care unit (NICU) admission, 5-minute Apgar score, birth weight, and PPH. Importantly, we stratified the analysis by singleton and multiple pregnancies to isolate the effects of ART from those of multifetal gestation, thereby providing clearer evidence for clinicians and patients.

2. Materials and Methods

2.1 Study Design and Participants

This retrospective cohort study was conducted at Gyeongsang National University Changwon Hospital, a tertiary referral center in South Korea, a tertiary referral center in South Korea. The study population consisted of all women who delivered live-born infants at the institution between January 2023 and December 2024. Maternal and neonatal data were retrospectively collected from electronic medical records, which included maternal demographic and clinical characteristics, obstetric history (e.g., parity and multifetal gestation), and perinatal and neonatal outcomes. Multiple pregnancies were restricted to twin gestations; triplet or higher-order gestations were excluded as they represent a heterogeneous group with significantly different outcomes.

2.2 Study Groups, Outcomes, and Covariates

The study population was stratified by pregnancy type into singleton and multiple pregnancies. Within each stratum, women who conceived through medically assisted techniques, including IVF, intracytoplasmic sperm injection (ICSI), or frozen embryo transfer, were classified as the ART group. The non-ART group included pregnancies conceived spontaneously, without the use of ART methods such as IVF, ICSI, or embryo transfer. Some women in the non-ART group may have received infertility-related interventions such as ovulation induction or intrauterine insemination; however, as these interventions do not involve extracorporeal manipulation of gametes or embryos, they were not classified as the ART group according to international standards [9]. Moreover, multiple pregnancies were analyzed as a separate cohort due to their distinct clinical characteristics and population risk profiles when compared to those of singleton pregnancies.

The primary outcomes assessed in this study included PTB (<37 weeks of gestation), small for gestational age (SGA), NICU admission, 5-minute Apgar score <7, neonatal death, and PPH. PPH was defined as a cumulative blood loss of ≥ 500 mL after vaginal delivery or ≥ 1000 mL following cesarean section [10], or based on intervention criteria indicative of significant hemorrhage, including blood transfusion, intrauterine balloon tamponade (IUBT), uterine artery embolization (UAE), or hysterectomy within 24 hours postpartum. SGA was defined as a birth weight be-

low the 10th percentile for gestational age. For singleton pregnancies, the INTERGROWTH-21st standard was used [11], whereas for multiple pregnancies, reference values from the Fetal Medicine Foundation twin-specific growth charts were applied [12].

In addition to neonatal outcomes, selected maternal pregnancy outcomes (short cervix, hypertensive disorders of pregnancy (HDP), and placenta previa) were included in the analysis to evaluate their potential association with ART. A short cervix was defined as a cervical length ≤ 25 mm measured by transvaginal ultrasound before 24 weeks of gestation [13]. HDP included gestational hypertension, preeclampsia, and eclampsia and were diagnosed according to American College of Obstetricians and Gynecologists (ACOG) guidelines [14] as new-onset hypertension after 20 weeks of gestation (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg). Placenta previa was defined as placental tissue reaching or covering the internal cervical os as visualized on ultrasound after 20 weeks of gestation, including total, partial, and low-lying placenta previa [15].

2.3 Statistical Analyses

Baseline maternal characteristics, obstetric complications, perinatal events, and neonatal outcomes were compared between the ART and non-ART groups within each gestational category (singleton and multiple pregnancies). Continuous variables (e.g., maternal age, gestational age at delivery, and birth weight) are presented as the mean $\pm$ standard deviation, and group comparisons were performed using Student's *t*-test or Welch's *t*-test depending on the equality of variances, which was assessed with Levene's test. Categorical variables (e.g., NICU admission, PTB, low Apgar scores, and neonatal death) are presented as the counts and percentage, and comparisons were made using chi-square test or Fisher's exact test as appropriate.

To assess the independent association between ART and each binary outcome, multivariable logistic regression models were constructed. The outcomes included PTB (<37 weeks), SGA, NICU admission, 5-minute Apgar score <7, neonatal death, and PPH. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated after adjusting for the following potential confounders: maternal age (years), pre-pregnancy body mass index (BMI, kg/m²), parity (nulliparous vs. multiparous), gestational diabetes mellitus (GDM), HDP, gestational age at delivery (weeks), and mode of delivery (cesarean vs. vaginal). Gestational age at delivery was excluded from the PTB model to avoid collinearity, as PTB is defined by gestational age. Sensitivity analyses were performed by excluding pregnancies with borderline gestational age (36+6 and 37+0 weeks) to evaluate the robustness of the primary findings. For multiple pregnancies, neonatal outcomes were evaluated at the pregnancy level. If either fetus experienced an adverse outcome (e.g., NICU admission, low Apgar scores,

and neonatal death), the pregnancy was classified as having the event. This approach was adopted to minimize statistical dependency between observations and to reflect the clinical management of twin gestations, which often focuses on the more severely affected fetus. Infrequent outcomes (e.g., 5-minute Apgar score <7, and neonatal death) were interpreted with caution due to the limited number of events, which may affect statistical power and model stability. To account for within-pregnancy correlation, particularly in twin births, additional analyses were performed using generalized estimating equations (GEE) with an exchangeable correlation structure were performed.

All statistical analyses were performed using Web-R ver. 3.4.1 (<http://web-r.org>), a web-based statistical analysis program. Additionally, R (R Foundation for Statistical Computing, Vienna, Austria; version 4.5.1) was used to reconstruct and verify results from the raw dataset. Statistical significance was defined as a two-sided p -value < 0.05. Forest plots were generated to visualize adjusted effect estimates.

3. Results

A total of 921 pregnancies were analyzed, comprising 816 singleton pregnancies (88.6%) and 105 multiple pregnancies (11.4%). Among singleton pregnancies, 175 pregnancies (21.4%) were conceived through ART, and 641 pregnancies (78.6%) were conceived spontaneously. Among multiple pregnancies, 78 pregnancies (74.3%) were conceived through ART, and 27 pregnancies (25.7%) occurred naturally. Maternal and neonatal characteristics grouped by ART exposure for singleton and multiple pregnancies are presented in Tables 1,2 respectively.

3.1 Singleton Pregnancies

Women with ART-conceived singleton pregnancies were significantly older (35.3 ± 3.8 vs. 33.1 ± 4.3 years, $p < 0.001$) and more often nulliparous (81.7% vs. 57.7%, $p < 0.001$) when compared to those with spontaneous conceptions. Pre-pregnancy BMI differed statistically between the ART and non-ART groups (24.1 ± 4.7 vs. 23.2 ± 4.7 , $p = 0.023$). BMI at delivery showed no significant difference between the groups ($p = 0.092$). The prevalence of short cervix was higher in the ART group (21.7% vs. 11.9%, $p = 0.001$); however, other pregnancy complications, such as GDM and HDP, showed no significant differences between the groups.

In terms of delivery outcomes, PPH occurred more frequently in ART-conceived singleton pregnancies (25.7% vs. 9.4%, $p < 0.001$). The ART group also showed increased use of intrauterine balloon tamponade (22.9% vs. 8.6%, $p < 0.001$) and a higher need for blood transfusion (5.7% vs. 2.3%, $p = 0.003$). Cesarean delivery was more frequent in the ART group (90.3% vs. 79.9%, $p = 0.001$), and placenta previa occurred more often (9.7% vs. 3.7%,

$p < 0.001$). The rates of ICU admission and other perinatal interventions did not differ significantly between the groups.

Neonatal outcomes, including gestational age at delivery (36.8 ± 3.0 vs. 36.8 ± 3.1 weeks, $p = 0.941$), birth weight (2817.1 ± 695.2 vs. 2773.2 ± 694.8 g, $p = 0.619$), 1-minute and 5-minute Apgar score (7.3 ± 1.2 vs. 7.4 ± 1.2 , $p = 0.367$; 8.5 ± 1.0 vs. 8.5 ± 1.0 , $p = 0.547$), and NICU admission (35.6% vs. 35.0%, $p = 0.722$), were comparable between the ART and non-ART groups. The incidence of SGA was also not significantly different between the groups (10.9% vs. 11.9%, $p = 0.705$). Neonatal death occurred in 3 ART pregnancies and 4 non-ART pregnancies, with no statistically significant difference ($p = 0.172$).

3.2 Multiple Pregnancies

In the multiple pregnancy cohort, women who conceived via ART were significantly older (34.7 ± 3.3 vs. 31.8 ± 3.1 years, $p < 0.001$) and more often primiparous (83.3% vs. 63.0%, $p = 0.027$) when compared to those with spontaneous conceptions. The proportion of monochorionic diamniotic (MCDA) twin gestations was lower in the ART group than in the non-ART group (10.3% vs. 29.6%, $p = 0.027$). Other maternal characteristics (including pre-pregnancy BMI and BMI at delivery) and pregnancy complications (e.g., short cervix, GDM, HDP, and placenta previa) did not differ significantly between the groups.

Cesarean section was the predominant mode of delivery in both groups, with no statistically significant difference (98.7% vs. 92.6%, $p = 0.162$). PPH was more frequent in the ART group but not statistically significant (28.2% vs. 22.2%, $p = 0.545$). Similarly, intrauterine balloon tamponade, blood transfusion, and ICU admission did not differ significantly.

Neonatal outcomes were largely comparable between ART and non-ART multiple pregnancies. The mean gestational age at delivery (35.2 ± 2.4 vs. 35.1 ± 2.4 weeks, $p = 0.846$), birth weight (2319.9 ± 448.8 vs. 2249.6 ± 404.5 g, $p = 0.448$), 1-minute and 5-minute Apgar score (7.2 ± 1.2 vs. 7.0 ± 1.3 , $p = 0.380$; 8.4 ± 0.9 vs. 8.2 ± 0.9 , $p = 0.339$), and NICU admission (41.0% vs. 50.0%, $p = 0.411$) did not differ significantly between the two groups. The incidence of SGA was also similar (14.1% vs. 14.3%, $p = 1.000$). Neonatal death was rare, occurred in 2 ART pregnancies and 1 non-ART pregnancy, with no statistically significant difference ($p = 1.000$). Taken together, ART use did not significantly affect key neonatal outcomes in multiple pregnancies. Additional GEE analyses to account for correlation between twins showed no significant associations between ART and neonatal outcomes, consistent with the primary results. Full results are provided in **Supplementary Table 1**.

Table 1. Comparison of maternal and neonatal characteristics between ART and non-ART pregnancies in the singleton pregnancy cohort.

Variables	ART (n = 175)	Non-ART (n = 641)	p-value
Maternal characteristics			
Age (years)	35.3 ± 3.8	33.1 ± 4.3	<0.001
Pre-pregnancy BMI (kg/m ²)	24.1 ± 4.7	23.2 ± 4.7	0.023
BMI at delivery (kg/m ²)	28.4 ± 4.7	27.8 ± 4.8	0.092
Primipara	143 (81.7%)	370 (57.7%)	<0.001
Pregnancy & perinatal outcomes			
Short cervix	38 (21.7%)	76 (11.9%)	0.001
Gestational diabetes mellitus	28 (16.0%)	81 (12.6%)	0.335
Hypertensive disorders of pregnancy	17 (9.7%)	48 (7.5%)	0.536
Cesarean delivery	158 (90.3%)	512 (79.9%)	0.001
Placenta previa	17 (9.7%)	24 (3.7%)	<0.001
Postpartum hemorrhage	45 (25.7%)	60 (9.4%)	<0.001
Blood transfusion	10 (5.7%)	15 (2.3%)	0.003
Intrauterine balloon tamponade	40 (22.9%)	55 (8.6%)	<0.001
Uterine artery embolization	2 (1.1%)	3 (0.5%)	0.288
Peripartum hysterectomy	0 (0.0%)	5 (0.8%)	0.584
Admission to ICU	0 (0.0%)	4 (0.6%)	0.584
Neonatal outcomes			
Gestational age at delivery (weeks)	36.8 ± 3.0	36.8 ± 3.1	0.941
Female newborn	85 (48.6%)	328 (51.2%)	0.601
Birth weight (g)	2817.1 ± 695.2	2773.2 ± 694.8	0.619
Small for gestational age	19 (10.9%)	76 (11.9%)	0.705
Apgar score at 1 minute	7.3 ± 1.2	7.4 ± 1.2	0.367
Apgar score at 5 minutes	8.5 ± 1.0	8.5 ± 1.0	0.547
Umbilical cord blood gas pH	7.3 ± 0.1	7.3 ± 0.1	0.102
Umbilical cord blood base excess (mmol/L)	−4.0 ± 2.5	−3.7 ± 2.3	0.187
Admission to NICU	62 (35.6%)	224 (35.0%)	0.722
Duration of NICU stay (days)	20.2 ± 22.3	26.8 ± 31.3	0.052
Respiratory support	67 (38.3%)	249 (39.0%)	0.825
Fetal malformation	32 (18.3%)	123 (19.2%)	0.845
Neonatal death	3 (1.7%)	4 (0.6%)	0.172

Data are presented as the mean ± standard deviation (SD) or as counts (percentages), as appropriate. Median (interquartile range, IQR) values for gestational age at delivery among singleton pregnancies were 37.5 (36.2–38.5) weeks in the ART group and 37.6 (35.6–38.4) weeks in the non-ART group. A *p*-value < 0.05 was considered statistically significant; significant values are shown in bold. Abbreviations: BMI, body mass index; ICU, intensive care unit; NICU, neonatal intensive care unit; ART, assisted reproductive technology.

3.3 Adjusted Associations Between ART and Pregnancy Outcomes

Multivariable logistic regression was performed to evaluate whether ART could independently predict adverse outcomes, adjusting for maternal age, pre-pregnancy BMI, parity, GDM, HDP, gestational age at delivery (excluded from the PTB model), and mode of delivery (Fig. 1 and Table 3).

In singleton pregnancies, ART was significantly associated with an increased risk of PPH (aOR: 3.64, 95% CI: 2.21–5.98, *p* < 0.001). No significant associations were found between ART and PTB (aOR: 0.91, 95% CI: 0.61–1.36, *p* = 0.647), SGA (aOR: 0.71, 95% CI: 0.39–1.29, *p*

= 0.256), NICU admission (aOR: 1.00, 95% CI: 0.69–1.44, *p* = 1.000), 5-minute Apgar score < 7 (aOR: 0.71, 95% CI: 0.24–2.10, *p* = 0.533), and neonatal death (aOR: 2.70, 95% CI: 0.39–18.52, *p* = 0.312). In a sensitivity analysis excluding borderline gestational age cases, the association between ART and PPH in singleton pregnancies remained statistically significant (aOR: 2.62, 95% CI: 1.60–4.29, *p* < 0.001), while the associations with PTB and NICU admission remained non-significant. Detailed results are shown in **Supplementary Table 2**.

In multiple pregnancies, none of the outcomes showed a statistically significant association with ART. Additionally, aORs for PTB (aOR: 1.62, 95% CI: 0.36–7.35, *p* =

Table 2. Comparison of maternal and neonatal characteristics between ART and non-ART pregnancies in the multiple pregnancy cohort.

Variables	ART (n = 78)	Non-ART (n = 27)	<i>p</i> -value
Maternal characteristics			
Age (years)	34.7 ± 3.3	31.8 ± 3.1	<0.001
Pre-pregnancy BMI (kg/m ²)	23.5 ± 4.7	22.6 ± 3.7	0.217
BMI at delivery (kg/m ²)	29.3 ± 4.8	28.4 ± 4.2	0.342
Primipara	65 (83.3%)	17 (63.0%)	0.027
DCDA twins	63 (80.8%)	19 (70.4%)	0.287
MCDA twins	8 (10.3%)	8 (29.6%)	0.027
Pregnancy & perinatal outcomes			
Short cervix	16 (20.5%)	2 (7.4%)	0.148
Gestational diabetes mellitus	13 (16.7%)	3 (11.1%)	0.757
Hypertensive disorders of pregnancy	7 (9.0%)	3 (11.1%)	0.715
Cesarean delivery	77 (98.7%)	25 (92.6%)	0.162
Placenta previa	1 (1.3%)	1 (3.7%)	0.450
Postpartum hemorrhage	22 (28.2%)	6 (22.2%)	0.545
Blood transfusion	7 (9.0%)	3 (11.1%)	0.715
Intrauterine balloon tamponade	20 (25.6%)	5 (18.5%)	0.454
Uterine artery embolization	3 (3.8%)	2 (7.4%)	0.601
Peripartum hysterectomy	1 (1.3%)	1 (3.7%)	0.450
Admission to ICU	1 (1.3%)	1 (3.7%)	0.450
Neonatal outcomes			
Gestational age at delivery (weeks)	35.2 ± 2.4	35.1 ± 2.4	0.846
Female newborn	39 (50.0%)	15 (53.6%)	0.746
Birth weight (g)	2319.9 ± 448.8	2249.6 ± 404.5	0.448
Small for gestational age	11 (14.1%)	4 (14.3%)	1.000
Apgar score at 1 minute	7.2 ± 1.2	7.0 ± 1.3	0.380
Apgar score at 5 minutes	8.4 ± 0.9	8.2 ± 0.9	0.339
Umbilical cord blood gas pH	7.3 ± 0.0	7.31 ± 0.1	0.656
Umbilical cord blood base Excess (mmol/L)	−4.3 ± 1.7	−4.9 ± 1.9	0.241
Admission to NICU	32 (41.0%)	14 (50.0%)	0.411
Duration of NICU stay (days)	18.2 ± 21.0	21.5 ± 22.6	0.651
Respiratory support	30 (38.5%)	11 (39.3%)	0.939
Fetal malformation	10 (12.8%)	3 (10.7%)	1.000
Neonatal death	2 (2.6%)	1 (3.6%)	1.000

Data are presented as the mean ± SD or as counts (percentages), as appropriate. Median (IQR) values for gestational age at delivery among twin pregnancies were 36.1 (35.2–36.5) weeks in the ART group and 35.8 (34.6–36.5) weeks in the non-ART group. A *p*-value < 0.05 was considered statistically significant; significant values are shown in bold. DCDA, dichorionic diamniotic; MCDA, monochorionic diamniotic.

0.533), SGA (aOR: 1.01, 95% CI: 0.25–4.10, *p* = 0.993), NICU admission (aOR: 0.39, 95% CI: 0.11–1.35, *p* = 0.136), and PPH (aOR: 2.53, 95% CI: 0.71–9.02, *p* = 0.152) were all found to be non-significant.

Logistic regression was not performed for 5-minute Apgar score <7 and neonatal death in multiple pregnancies due to insufficient event frequency. Specifically, no cases of Apgar score <7 were observed in the non-ART group, and only 3 neonatal deaths occurred in the entire multiple pregnancy cohort, precluding reliable estimation.

4. Discussion

This study evaluated the obstetric, perinatal, and short-term neonatal outcomes of pregnancies conceived via ART compared to those conceived spontaneously, with analyses stratified by singleton and multiple pregnancies. Overall, most obstetric complications and neonatal outcomes were comparable between the ART and non-ART groups. However, ART-conceived singleton pregnancies demonstrated higher rates of short cervix and PPH. In comparison to women in the non-ART group, those in the ART group were also older and more likely to be nulliparous. In the multiple pregnancy cohort, ART pregnancies showed

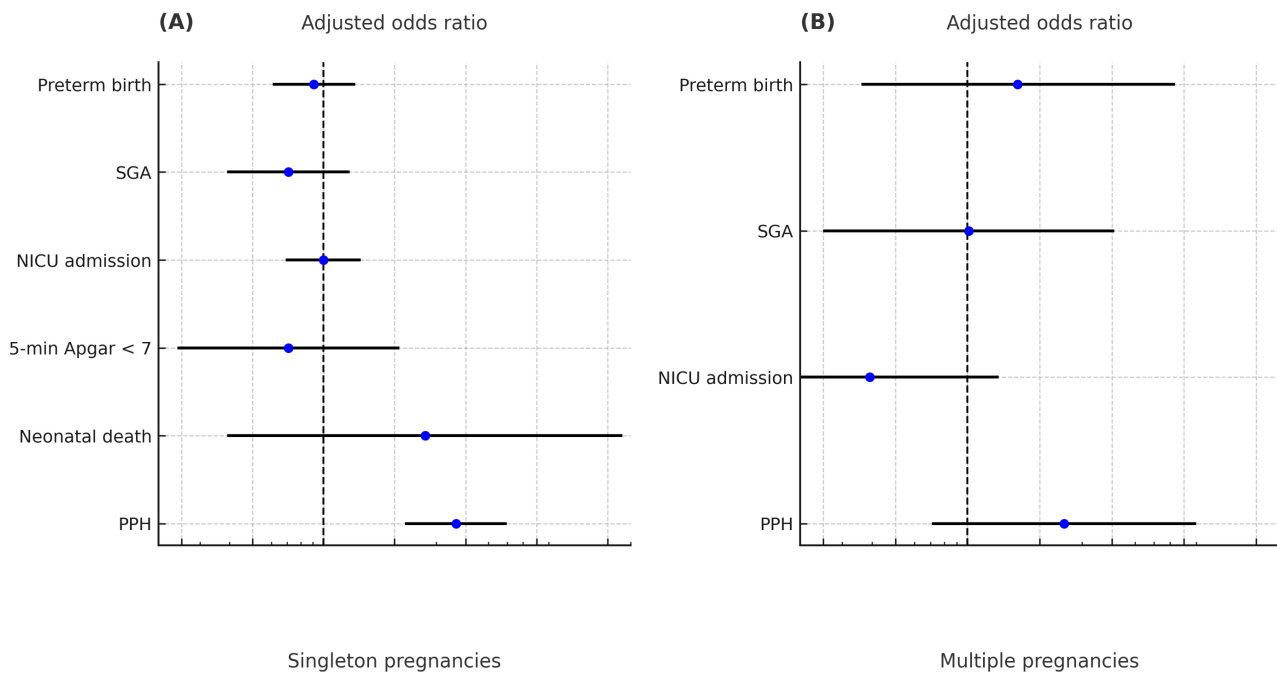


Fig. 1. Forest plot showing the association between ART and adverse obstetric and neonatal outcomes in (A) singleton and (B) multiple pregnancies. The vertical dashed line represents an odds ratio of 1. Adjusted odds ratios (aORs, blue dot) and 95% confidence intervals (CIs, error bars) were calculated by multivariable logistic regression with adjustment for maternal age, pre-pregnancy BMI, parity, GDM, HDP, gestational age at delivery, and mode of delivery. Gestational age at delivery was excluded from the PTB model. SGA, small for gestational age; PPH, postpartum hemorrhage; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy; PTB, preterm birth.

a lower proportion of MCDA twins. Multivariable logistic regression revealed that ART was not independently associated with adverse short-term perinatal or neonatal outcomes, except for an increased risk of PPH in singleton pregnancies.

Previous studies have reported elevated risks of obstetric and perinatal complications associated with ART. Chen *et al.* [4] demonstrated significantly higher rates of PTB, NICU admission, low birth weight, and PPH in the ART group compared to the spontaneously conceived group, with differences persisting even after adjusting for confounders. Similarly, a single-center study by Marsubrin *et al.* [2] observed higher incidences of PTB, respiratory distress syndrome, and NICU admission, along with longer hospitalization, among ART-conceived neonates compared to those conceived naturally.

In contrast, this study did not show significant differences in PTB, low birth weight, NICU admission, and Apgar score between the ART and non-ART groups, particularly in the analysis of singleton pregnancies. Apart from the elevated risk of PPH and short cervix, ART was not identified as an independent risk factor for short-term perinatal morbidity. These findings remained consistent in sensitivity analyses excluding borderline gestational age cases, supporting the robustness of the results. These contrasting results may be attributed to key differences in study design

and population characteristics. In both prior studies, the ART group included a higher proportion of multiple gestations, a well-established risk factor for adverse neonatal outcomes. For instance, Marsubrin *et al.* [2] reported that approximately 38% of ART pregnancies were multifetal, which may have contributed to the higher rates of preterm birth and NICU admission observed in that study. In this analysis, we stratified outcomes by plurality and focused primarily on singleton pregnancies, thereby minimizing the confounding impact of multiple gestation.

While Chen *et al.* [4] used multicenter data and Marsubrin *et al.* [2] conducted a single-center study, both studies offered limited detail on how maternal variables and outcome definitions were standardized across their datasets. In contrast, this study utilized electronic medical record data from a single tertiary institution, where definitions and measurement protocols were applied consistently. We conducted multivariable logistic regression controlling for maternal age, BMI, parity, and major medical conditions such as hypertension and diabetes, allowing more rigorous adjustment for potential confounders. These differences suggest that the risks associated with ART may vary depending on maternal characteristics, the clinical environment, and how outcomes are defined and analyzed. The present finding supports the view that ART may not independently contribute to short-term perinatal morbidity when appro-

Table 3. Adjusted odds ratios (aORs) for adverse pregnancy and neonatal outcomes associated with ART in singleton and multiple pregnancies.

Outcomes	Singleton aOR (95% CI)	p-value	Multiple aOR (95% CI)	p-value
Preterm birth (<37 weeks)	0.91 (0.61–1.36)	0.647	1.62 (0.36–7.35)	0.533
SGA	0.71 (0.39–1.29)	0.256	1.01 (0.25–4.10)	0.993
NICU admission	1.00 (0.69–1.44)	1.000	0.39 (0.11–1.35)	0.136
5-minute Apgar score <7	0.71 (0.24–2.10)	0.533	—	—
Neonatal death	2.70 (0.39–18.52)	0.312	—	—
PPH	3.64 (2.21–5.98)	<0.001	2.53 (0.71–9.02)	0.152

Multivariable logistic regression models were adjusted for maternal age, pre-pregnancy BMI, parity, GDM, HDP, gestational age at delivery (excluded in the PTB model), and mode of delivery.

Adjusted analyses for 5-minute Apgar score <7 and neonatal death in multiple pregnancies were not performed due to sparse events and unstable estimates. Bold values indicate statistical significance at $p < 0.05$. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

appropriately adjusted and evaluated within a contemporary and controlled clinical setting.

The findings reflect limitations in earlier studies, many of which did not sufficiently adjust for critical confounding factors such as maternal age, multifetal gestation, and baseline comorbidities. In a sibling cohort study comparing ART and naturally conceived pregnancies, Romundstad *et al.* [16] reported that differences in birth weight and preterm delivery largely disappeared or lost statistical significance after controlling for maternal demographics and health factors. Similarly, a population-based analysis in the United States [17] found that although ART pregnancies were initially associated with higher rates of PTB and low birth weight, these elevated risks were attenuated when focusing on singleton gestations and adjusting for maternal characteristics.

Pandey *et al.* [3] reported increased perinatal risks in ART-conceived singleton births in a meta-analysis. However, these findings may partially reflect earlier ART protocols, such as frequent multiple embryo transfers and less advanced embryo culture methods. Differences in study populations or unmeasured residual confounding related to subfertility may also contribute to these discrepancies. In contrast, this study is based on recent clinical data and thus reflects contemporary ART practice, such as elective single embryo transfer and improved obstetric surveillance [18]. The consistent clinical environment of this single-center cohort may have minimized variability and confounding, though at the cost of generalizability and reduced power to detect small effects. Overall, these contrasting findings reflect improvements in ART safety over time, emphasizing the need to re-evaluate ART-associated risks in the context of modern practice through updated, large-scale studies.

Despite the overall reassuring results, this study found a significantly higher rate of PPH among ART-conceived singleton pregnancies. This finding is consistent with prior research identifying ART as a risk factor for PPH and related interventions such as blood transfusion [19]. This elevated risk is thought to result from multiple pathophysio-

logical mechanisms, such as abnormal placental implantation, impaired vascular development due to hormonal stimulation, and uterine atony. In this cohort, the incidence of PPH in the ART group was high at 25.7% compared to 9.4% in the non-ART group. ART pregnancies also required more interventions for bleeding control, including intrauterine balloon tamponade and blood transfusion.

Although previous studies have reported PPH rates of approximately 11.1–19.2% in ART pregnancies [4,19], the incidence observed in the present study's ART-conceived singleton cohort was comparatively higher (25.7%). This may reflect the high-risk nature of the study population and differences in diagnostic criteria and surveillance methods. In this study, PPH was defined as clinically significant bleeding or an estimated blood loss of ≥ 500 mL after vaginal delivery or ≥ 1000 mL after cesarean section. This threshold differs from those used in prior studies that applied a uniform definition of ≥ 1000 mL regardless of delivery mode [20], potentially contributing to the higher detection rate in this cohort. Quantitative blood loss (QBL) measurement is routinely implemented for all deliveries at the study hospital, including both vaginal and cesarean births. The measurement process involves the use of graduated drapes for real-time blood collection, weighing of all blood-soaked materials, and adjustment for irrigation fluid in suction canisters. Compared with visual estimation, this standardized approach improves measurement accuracy and facilitates earlier recognition of hemorrhage. Furthermore, all postpartum patients are managed under an enhanced surveillance protocol that includes frequent monitoring of vital signs, uterine tone, lochia, and urine output during the first 24 hours after delivery. This comprehensive monitoring system may have increased the sensitivity of PPH detection in the present cohort. The higher rate of bleeding-related interventions observed in the ART group reinforces the clinical importance of these findings. Consistency in measurement and monitoring protocols likely enabled the identification of PPH cases that might have gone unrecognized in studies with less structured methods. Collectively,

these results support the classification of ART pregnancies as a population at elevated risk for PPH, underscoring the importance of vigilant monitoring and proactive clinical management in this group.

Another notable finding was the increased incidence of short cervical length in singleton pregnancies conceived via ART. This may reflect procedural factors (e.g., cervical instrumentation during embryo transfer or prior uterine procedures), as well as underlying infertility-related conditions (e.g., congenital uterine anomalies, polycystic ovary syndrome, or previous surgical curettage), which are more prevalent in ART populations [21,22]. These conditions are independently associated with cervical insufficiency and PTB. Therefore, routine mid-trimester cervical length screening should be considered in ART-conceived singleton pregnancies regardless of obstetric history. Early detection can facilitate timely interventions such as progesterone therapy or cervical cerclage when indicated.

Taken together, the present findings are reassuring for women conceiving via ART. With proper management, ART pregnancies may achieve perinatal outcomes comparable to those of spontaneous conceptions. Importantly, ART itself does not appear to be an intrinsic risk factor for most adverse outcomes; rather, associated risks often stem from modifiable contributors such as multifetal gestation and maternal comorbidities. In particular, preventing multiple pregnancies is a key strategy in mitigating ART-related risks. Elective single embryo transfer has been shown to reduce the incidence of twin gestations without compromising live birth rates [23]. Minimizing iatrogenic multiple births allows clinicians to significantly reduce PTB and other complications linked to ART. Additionally, optimizing maternal health, such as managing chronic hypertension or diabetes, during ART pregnancies can improve outcomes and address negative perceptions about infertility treatments. Current evidence suggests that ART, when practiced according to modern protocols, does not inherently jeopardize perinatal health. This information may help reduce patient anxiety and promote more informed and confident decision-making.

This study has several limitations. It was conducted retrospectively at a single tertiary medical center, with a modest sample size and a two-year inclusion period. These factors may have limited the ability of the study to detect rare events such as perinatal mortality or long-term neonatal sequelae. In particular, the very small number of neonatal death events, especially in the multiple pregnancy cohort, may have limited the statistical power to detect meaningful differences for this outcome. Additionally, we were unable to compare outcomes across different ART modalities (e.g., IVF vs. ICSI) or fully control for all potential confounders, such as specific infertility diagnoses, socioeconomic status, and maternal lifestyle factors. These unmeasured variables may have influenced the observed associations and should be considered when interpreting the findings. ART-related

factors such as ovarian stimulation protocols, embryo transfer methods, and infertility etiology could not be assessed in this study due to lack of available information. These variables may influence outcomes such as postpartum hemorrhage and cervical length and warrant further investigation in studies with more detailed ART data. As an observational study, causality could not be established, and residual confounding from unmeasured variables may persist despite adjustment.

Nevertheless, this study has certain methodological strengths. Notably, we analyzed singleton and multiple pregnancies separately, allowing for a more accurate estimation of the effects of ART independent of plurality—a critical confounder in ART research. By stratifying analyses in this manner, we reduced the bias from the overrepresentation of multifetal gestation in ART populations and avoided misleading comparisons between heterogeneous pregnancy types. Moreover, all data were obtained from a single institution with standardized clinical protocols, ensuring consistency in diagnosis, management, and documentation. We also used multivariable logistic regression models to adjust for key maternal and obstetric factors, enhancing the internal validity of our findings. Moving forward, larger multicenter studies with long-term follow-up are needed to assess delayed or subtle outcomes in ART-conceived offspring and better evaluate the safety profile of different ART modalities. Such studies will support more robust, evidence-based counseling and enhance care for individuals pursuing ART.

5. Conclusions

In conclusion, this study demonstrated that conception via ART was not independently associated with increased risks of major perinatal or neonatal complications after adjusting for maternal and obstetric confounders. The elevated risks traditionally attributed to ART appeared to stem primarily from multifetal gestation and maternal health factors, rather than ART procedures. The findings underscore the importance of targeted strategies to mitigate risks in ART pregnancies—specifically, the prevention of multifetal gestation and proactive management of maternal comorbidities. By implementing such strategies, the outcomes of ART pregnancies can approach those of spontaneously conceived pregnancies. Continued emphasis on promoting singleton pregnancies and optimizing perinatal care is essential for improving the safety and success of ART. Future research should focus on long-term neonatal outcomes and the comparative safety of specific ART modalities to further inform clinical practice and patient counseling.

Availability of Data and Materials

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

Author Contributions

JEP designed the research study. JY, HCJ, and JEP performed the research. JCB contributed to data acquisition and part of the data analysis process. JY, HCJ, and JEP analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors participated in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This cohort study was approved by the Ethics Committee of Gyeongsang National University Changwon Hospital (IRB number: GNUCH 2025-07-023) and was conducted according to the principles of the Declaration of Helsinki. Informed consent was waived by the Ethics Committee because of the use of retrospective and deidentified data.

Acknowledgment

The authors would like to thank the staff and patients of Gyeongsang National University Changwon Hospital for their cooperation and support.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The authors declare that AI-assisted technologies, specifically OpenAI's ChatGPT, were used to support the writing process of this manuscript. The tool was employed solely for language refinement and grammar correction. All intellectual contributions, data interpretation, and conclusions presented in this manuscript were made by the authors. The use of AI was strictly for enhancing the manuscript's presentation and did not influence the scientific content or the integrity of the research. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/CEOG45477>.

References

- [1] Adamson GD, Creighton P, de Mouzon J, Zegers-Hochschild F, Dyer S, Chambers GM. How many infants have been born with the help of assisted reproductive technology? *Fertility and Sterility*. 2025; 124: 40–50. <https://doi.org/10.1016/j.fertnstert.2025.02.009>.
- [2] Marsubrin PMT, Sugiyarto KLJ, Oswari JS, Rohsiswatmo R, Roeslani RD, Iskandar ATP, *et al.* Single-centre comparative study of *in vitro* fertilisation and naturally conceived babies in Indonesia. *BMJ Paediatrics Open*. 2025; 9: e003142. <https://doi.org/10.1136/bmjpo-2024-003142>.
- [3] Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Human Reproduction Update*. 2012; 18: 485–503. <https://doi.org/10.1093/humupd/dms018>.
- [4] Chen Y, Zhang M, Gao Y, Li M, Zheng W, Guo X, *et al.* Perinatal complications and neonatal outcomes in *in vitro* fertilization/intracytoplasmic sperm injection: a propensity score matching cohort study. *Frontiers in Endocrinology*. 2024; 15: 1405550. <https://doi.org/10.3389/fendo.2024.1405550>.
- [5] Ganer Herman H, Mizrachi Y, Shevach Alon A, Farhadian Y, Gluck O, Bar J, *et al.* Obstetric and perinatal outcomes of *in vitro* fertilization and natural pregnancies in the same mother. *Fertility and Sterility*. 2021; 115: 940–946. <https://doi.org/10.1016/j.fertnstert.2020.10.060>.
- [6] Prats P, Zarragoitia J, Rodríguez MÁ, Rodríguez I, Martínez F, Rodríguez-Melcon A, *et al.* Outcome in a series of 1135 twin pregnancies: does the type of conception play a role? *AJOG Global Reports*. 2022; 2: 100129. <https://doi.org/10.1016/j.xagor.2022.100129>.
- [7] Wennberg AL, Opdahl S, Bergh C, Aaris Henningsen AK, Gissler M, Romundstad LB, *et al.* Effect of maternal age on maternal and neonatal outcomes after assisted reproductive technology. *Fertility and Sterility*. 2016; 106: 1142–1149.e14. <https://doi.org/10.1016/j.fertnstert.2016.06.021>.
- [8] Tai W, Hu L, Wen J. Maternal and Neonatal Outcomes After Assisted Reproductive Technology: A Retrospective Cohort Study in China. *Frontiers in Medicine*. 2022; 9: 837762. <https://doi.org/10.3389/fmed.2022.837762>.
- [9] Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, *et al.* The International Glossary on Infertility and Fertility Care, 2017. *Human Reproduction* (Oxford, England). 2017; 32: 1786–1801. <https://doi.org/10.1093/humrep/dex234>.
- [10] Dahlke JD, Mendez-Figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, *et al.* Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *American Journal of Obstetrics and Gynecology*. 2015; 213: 76.e1–76.e10. <https://doi.org/10.1016/j.ajog.2015.02.023>.
- [11] Papageorgiou AT, Kennedy SH, Salomon LJ, Altman DG, Ohuma EO, Stones W, *et al.* The INTERGROWTH-21st fetal growth standards: toward the global integration of pregnancy and pediatric care. *American Journal of Obstetrics and Gynecology*. 2018; 218: S630–S640. <https://doi.org/10.1016/j.ajog.2018.01.011>.
- [12] Wright A, Wright D, Chaveeva P, Molina FS, Akolekar R, Syngelaki A, *et al.* Fetal Medicine Foundation charts for fetal growth in twins. *Ultrasound in Obstetrics & Gynecology: the Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2024; 63: 181–188. <https://doi.org/10.1002/ulog.27514>.
- [13] Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. *Obstetrics and Gynecology*. 2021; 138: e65–e90. <https://doi.org/10.1097/AOG.0000000000004479>.
- [14] Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstetrics and Gynecology*. 2020; 135: e237–e260. <https://doi.org/10.1097/AOG.0000000000003891>.
- [15] Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. *Obstetrics and Gynecology*. 2006; 107: 927–941. <https://doi.org/10.1097/01.AOG.0000207559.15715.98>.

- [16] Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Gunnell D, *et al.* Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. *Lancet* (London, England). 2008; 372: 737–743. [https://doi.org/10.1016/S0140-6736\(08\)61041-7](https://doi.org/10.1016/S0140-6736(08)61041-7).
- [17] Wang R, Shi Q, Jia B, Zhang W, Zhang H, Shan Y, *et al.* Association of Preterm Singleton Birth With Fertility Treatment in the US. *JAMA Network Open*. 2022; 5: e2147782. <https://doi.org/10.1001/jamanetworkopen.2021.47782>.
- [18] ESHRE Guideline Group on the Number of Embryos to Transfer, Alteri A, Arroyo G, Baccino G, Craciunas L, De Geyter C, *et al.* ESHRE guideline: number of embryos to transfer during IVF/ICSI†. *Human Reproduction* (Oxford, England). 2024; 39: 647–657. <https://doi.org/10.1093/humrep/deae010>.
- [19] Solmonovich R, Kouba I, Jackson FI, Alvarez A, Goldman RH, San Roman G, *et al.* Association of in vitro fertilization with severe maternal morbidity in low-risk patients without comorbidities. *Fertility and Sterility*. 2025; 123: 262–269. <https://doi.org/10.1016/j.fertnstert.2024.09.015>.
- [20] Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 183: Postpartum Hemorrhage. *Obstetrics and Gynecology*. 2017; 130: e168–e186. <https://doi.org/10.1097/AOG.0000000000002351>.
- [21] Meng L, Öberg S, Sandström A, Reilly M. Association between infertility and cervical insufficiency in nulliparous women-the contribution of fertility treatment. *American Journal of Obstetrics and Gynecology*. 2025; 232: 468.e1–468.e9. <https://doi.org/10.1016/j.ajog.2024.10.035>.
- [22] Wu Y, Cai M, Liang X, Yang X. The prevalence of cervical insufficiency in Chinese women with polycystic ovary syndrome undergone ART treatment accompanied with negative prognosis: a retrospective study. *Journal of Obstetrics and Gynaecology: the Journal of the Institute of Obstetrics and Gynaecology*. 2021; 41: 888–892. <https://doi.org/10.1080/01443615.2020.1819212>.
- [23] Lee AM, Connell MT, Csokmay JM, Styer AK. Elective single embryo transfer- the power of one. *Contraception and Reproductive Medicine*. 2016; 1: 11. <https://doi.org/10.1186/s40834-016-0023-4>.