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The Effect of Assisted Reproductive Technology on Morbidity and Mortality of Twin Premature — A Secondary Publication

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Abstract: *Objective:* It is thought that twin neonates born from pregnancies resulting from assisted reproductive technology (ART) are clinically riskier than twin neonates born from spontaneous pregnancy. However, information on the risks in premature infants born as a result of ART pregnancies is limited. In our study, premature twin infants born from ART and spontaneous pregnancies were compared to clinical outcomes. *Method:* All premature twin infants hospitalized in our unit between September 2017 and September 2019 and born under 32 weeks of gestation were included in our study. Demographic and clinical results of premature twins born as a result of spontaneous and ART pregnancies were compared. *Results:* A total of 142 premature twins, 116 (81.6%) in the spontaneous twin group and 26 (18.4%) in the ART twin group, were included in the study. Demographic and clinical features were similar between ART and spontaneous twin groups ($P > 0.05$). *Conclusion:* Our study determined that premature infants born due to ART pregnancies did not have any additional risk compared to spontaneous infants. This result shows that the main determinants of clinical outcomes in premature infants are gestational week and birth weight.

Keywords: Premature; Twin; Morbidity; Mortality; Assisted reproductive technique

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1. Introduction

Pregnancy rates have increased with the introduction of assisted reproductive techniques (ART) in the last forty years. Additionally, ART has caused the incidence of twin births to increase to 1–4%. Although it causes an increase in pregnancy rates, the older age of mothers who become pregnant as a result of ART, the use of high doses of medication, and the transfer of more than one embryo may also cause some negative consequences. There is an increased risk of gestational diabetes, gestational hypertension, and preeclampsia in women who become pregnant as a result of ART. In addition, it also brings with it an increased risk of premature birth and the risks associated with prematurity [1].

Approximately 1 in 10 twins are born before the 32nd week of gestation (GH). The increased risk of preterm birth with ART causes an increase in the number of premature babies born < 32 GW, which is at

greater risk for morbidity and mortality [2]. It is still unclear whether twin babies born after ART or spontaneous pregnancy at the same GW will change perinatal outcomes. Generally, in ART and spontaneous twin studies, it is 22–42. The outcomes of babies born at a wide range of GH, such as GH, have been evaluated [1,3]. The issue of whether premature twin babies born at < 32 GH, which are particularly at risk for morbidity and mortality, and resulting from ART, are at risk compared to spontaneous twin babies, has not been adequately investigated. Therefore, our study aimed to compare the clinical outcomes of premature twin babies born below the 32nd GW after ART and spontaneous pregnancies.

2. Materials and methods

2.1. Study design

Our study was conducted as a retrospective cohort among premature babies admitted to our neonatal intensive care unit (NICU) between September 2017 and September 2019. All premature twin babies born at gestational age < 32 weeks were included in the study. Singleton and triplet babies with major congenital anomalies and babies born at ≥ 32 GH were excluded from the study. Premature twin babies included in the study were divided into groups as ART and spontaneous twins according to the type of pregnancy.

Demographic and clinical characteristics of all patients were obtained from medical records. Approval was obtained from the local ethics committee before the study. This study was conducted in accordance with the Declaration of Helsinki Principles.

2.2. Demographic and clinical characteristics

In the ART and spontaneous twin groups, maternal age, GH, birth weight (BW), gender, low birth weight for gestational age (SGA; small for gestational age)[4], maternal hypertension/diabetes, antenatal steroid administration, delivery method (cesarean or vaginal birth), 1st and 5th minute Apgar score, early neonatal sepsis (ENS; sepsis ≤ 3 days postnatal), late neonatal sepsis (GNS; sepsis > 3 days postnatal)[5], respiratory distress syndrome (RDS)[6], oxygen duration of support need non-invasive duration of ventilation (NIV) and invasive MV, bronchopulmonary dysplasia (BPD; moderate/severe)[7], retinopathy of prematurity (ROP) requiring treatment [8], intraventricular hemorrhage (IVH) (Stage ≥ 3)[9], necrotizing enterocolitis (NEC) (Stage ≥ 2)[10], hemodynamically significant patent ductus arteriosus (PDA)[11], time to transition to full enteral nutrition, NICU stay, and mortality were recorded. ART and spontaneous twin groups were compared in terms of demographic and clinical characteristics.

2.3. Statistical analysis

Demographic and clinical data obtained from medical records were transferred to the computer environment. Statistical analyses were performed using SPSS 16.0 statistical program. The conformity of the measured values to normal distribution was determined both graphically and by the Shapiro-Wilk test. Results are presented as mean ± standard deviation or median (minimum-maximum). For continuous variables, the *t*-test or Mann-Whitney U test was applied. For nominal variables, the χ^2 test or Fisher exact test was applied. If the *P* value was < 0.05, it was considered statistically significant.

3. Results

A total of 142 twin premature babies (GW: 28 ± 1.1 weeks, BM: 1083 ± 218 g) were included in the study. 116 (81.6%) premature babies were included in the spontaneous twin group and 26 (18.4%) premature babies in the

ART twin group. No significant difference was detected between the ART twin and spontaneous twin groups in terms of demographic and clinical characteristics ($P > 0.05$). The statistical analysis results of the data are given in **Tables 1 & 2**.

Table 1. Demographic characteristics of the study groups

Variables	Spontaneous twin group (*n* = 116, 81.6%)	ART twin group (*n* = 26, 18.4%)	*P*
Maternal age (years)	28 ± 5.6	30.8 ± 6.9	0.218
Maternal hypertension, *n* (%)	0 (0)	1 (3.8)	0.327
Maternal diabetes, *n* (%)	4 (3.4)	0 (0)	0.340
Antenatal steroids, *n* (%)	73 (63)	18 (69)	0.718
Gestational age (weeks, [a])	28.1 ± 11	27.7 ± 1.2	0.564
Birth weight, (g,[a])	1069 ± 218	1145 ± 212	0.110
SGA, *n* (%)	10 (8.6)	1 (3.8)	0.310
Cesarean section, *n* (%)	112 (96.5)	26 (100)	0.1441
Apgar score, [b]	5 (2)	5 (2)	0.7565
Apgar score, [b]	7 (2)	7 (2)	
Male gender, *n* (%)	60 (51.7)	15 (57.6)	0.588

Note: [a] mean ± standard deviation, [b] median (interquartile range) ART, assisted reproductive technique; SGA: low birth weight for gestational age

Table 2. Comparison of the study groups in terms of clinical characteristics

Variables	Spontaneous twin group (*n* = 116, 81.6%)	ART twin group (*n* = 26, 18.4%)	*P*
ENS, *n* (%)	3 (2.5)	0 (0)	0.083
GNS, *n* (%)	21 (18.1)	5 (19.2)	0.908
RDS, *n*	88 (75.8)	19 (73)	0.776
Oxygen requirement (per day)	25.6 ± 12.4	22.5 ± 16.7	0.437
NIV duration (days, [a])	7.9 ± 5.9	6.9 ± 4.4	0.523
MV duration (days, [a])	3.0 ± 2.7	2.7 ± 2.2	0.119
BPD, *n*	20 (17.2)	6 (23)	0.208
ROP, *n*	11 (9.4)	1 (3.8)	0.090
IVK, Stage ≥ 3, *n* (%)	16 (13.7)	3 (11.5)	0.473
NEC, Stage ≥ 2, *n* (%)	2 (1.7)	0 (0)	0.158
PDA, *n* (%)	57 (49.1)	15 (57.6)	0.086
Complete enteral nutrition (days, [a])	15.8 ± 6.3	14.8 ± 3.7	0.440
NICU length of stay (days, [a])	54.3 ± 31.75	53.3 ± 22.6	0.858
Mortality, *n* (%)	21 (18.1)	3 (11.5)	0.195

Note: [a] Mean ± standard deviation, ART, assisted reproductive technique; BPD, bronchopulmonary dysplasia; ENS, early neonatal sepsis; IVH, intraventricular hemorrhage; MV, mechanical ventilation; GNS, late neonatal sepsis; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NIV, non-invasive ventilation; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

4. Discussion

In our study, premature twin pregnancies below 32 weeks gestation were evaluated. Our premature patient population at < 32 weeks gestation, which is riskier in terms of morbidity and mortality compared to term, early term ($37^{0/7}$–$38^{6/7}$ weeks), and late preterm ($34^{0/7}$–$36^{6/7}$ weeks) babies, were divided into groups as ART twins and spontaneous twins. The demographic characteristics and clinical outcomes including morbidity and mortality were similar between the groups.

Güler *et al.* reported that 66.6% of twin babies were born as a result of ART pregnancies and 33.4% were born as a result of spontaneous pregnancies [12]. In our results, the rate of ART was 18.4% and the rate of spontaneous twins was 81.6%. This rate may be influenced by the frequency of ART practice in the centers, the follow-up protocol of the perinatology clinic, and the level of technology of the center. Twin pregnancies are considered risky pregnancies due to high maternal and perinatal mortality. Since the frequency of twin pregnancies after ART increases, an increase in premature birth and related risks may be observed [12,13]. In fact, it has been reported that multiple babies born as a result of ART pregnancies are hospitalized in the intensive care unit for longer periods and have more serious problems and higher treatment costs [14]. Although there have been studies comparing ART and spontaneous twins, the results of these studies differ from one another.

While some studies indicate that maternal and fetal outcomes of multiple pregnancies following ART there are also studies showing no statistically significant difference. These studies often evaluate pregnancies at term, near term, or across all gestational ages [1,3,12,15]. More specifically, studies evaluating the effect of ART pregnancies on the morbidity and mortality of premature deliveries at < 32 GA are limited.

The maternal age of ART mothers was higher than those of spontaneous birth. This is due to the fact that mothers who cannot have a baby at a young age become pregnant with ART at an older age [1,16]. In our study, although maternal age was higher in the ART group, no statistically significant difference was found. Similar results have been obtained in other clinical studies [12,17].

In the literature, the rate of cesarean delivery has been reported to be higher in ART pregnancies compared to spontaneous multiple pregnancies [18,19]. Similar to our results, studies conducted in our country also found high rates of cesarean delivery in ART and spontaneous twin pregnancies, but these rates were reported to be similar between the groups [12,20]. The reason for this is that multiple pregnancies are often seen as an indication of cesarean delivery.

The risk of maternal morbidity may increase in premature babies born as a result of ART pregnancies. However, as in our study, ART may not increase the risk of maternal disease. The possible reason for the lack of difference between the groups in terms of maternal diseases may be that maternal diseases occur more frequently in the 3rd trimester. Since our study group patients were not in the 3rd trimester, the results in terms of maternal diseases may have been similar [1,13,21]. In addition, GH and DA were found to be similar in the groups. However, some studies have reported that GH and DA were lower in ART pregnancies. In ART pregnancies, there will be an increase in preterm labor due to increased maternal disease and placental risks in the 3rd trimester, increased maternal and fetal risks, and preterm delivery, which will lead to lower GH and DA [1,13,22]. We think that GH and DA were similar in the ART and spontaneous twin groups due to similar maternal and fetal risks in our study population. Our results are similar to some previous studies [12,23,24].

Perinatal morbidity and mortality are inversely related to GH [25]. The effect of ART, especially at < 32 GH, is not fully known [26]. In terms of mortality, neonates born to ART pregnancies have been reported to be at higher risk for morbidity and mortality. However, this may change as GH decreases. Twin premature twins from ART pregnancies may have lower perinatal mortality than spontaneous twins. The possible reason may be that twins from ART pregnancies are born as monozygotic twins at a lower rate than spontaneous twins. This

is explained by the higher incidence of twin-to-twin transfusion syndrome in monochorionic twins compared to dichorionic twins [26]. In our data, mono/dichorionic information is unknown. Although ART pregnancies increase the risk of prematurity, there may not be an increased mortality compared to spontaneous twins with the same GA [3,26]. Our results support this information. Therefore, the main factor affecting mortality, especially in premature infants, is GH and DA rather than ART [3,26].

Babies with very low birth weight, which is our current patient population, are at risk for many morbidities (RDS, BPD, ROP, IVK, NEC, PDA, etc.) [25]. In addition to the advances in current treatment approaches and the risk of prematurity, it is still unclear whether twins born from ART pregnancies carry an additional risk for morbidity compared to spontaneous twins [26,27]. In a study examining all GA, the results were similar in terms of RDS, MV, mortality, and severe morbidity in twins born as a result of ART pregnancy and twins born from spontaneous pregnancy [3]. More specifically, there is insufficient information on the relationship between morbidity and ART at < 32 GA.

In our study, we concluded that being a twin after ART or spontaneous pregnancy did not pose a risk for the morbidity of prematurity in pre-terms born at < 32 GH. This may be because this group of pre-terms did not experience the third trimester and were not affected by maternal and placental factors. In addition, the fact that the main risks affecting the morbidity and mortality of prematurity such as antenatal steroids, GH, and DA were similar in the groups explains the similar clinical outcomes in both groups. According to our results, these babies born with similar prenatal risk factors and having similar postnatal care conditions face similar clinical outcomes due to similar GH and DA, regardless of whether they are ART or spontaneous twins.

Our study has limitations because it was single-centered, retrospective, and had a small sample size. In addition, data such as the technique of ART, twin-twin transfusion, mono- or dichorionic information, and placental pathology are missing.

5 Conclusion

In conclusion, some adverse clinical outcomes may be seen in infants born after ART pregnancies. However, our results showed that premature twins below 32 GH born from ART pregnancies had no additional risk compared to spontaneous twins. Considering that there is insufficient information on the effect of ART on morbidity and mortality especially in very low birth weight premature infants, studies with larger series should be conducted in this group of patients.

Author contribution

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Disclosure statement

The authors declare no conflict of interest.

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