



Maternal and Neonatal Outcomes of Monochorionic and Dichorionic Twin Pregnancies Following Assisted Reproductive Technology in Southern Iranian Women

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Abstract

Objectives: This study aimed to investigate the effect of assisted reproductive technology (ART) on both maternal and neonatal outcomes in monochorionic (MC) and dichorionic (DC) twin pregnancies.

Methods: This retrospective cohort study was conducted on women with twin pregnancies who delivered at Hafez and Hazrat Zeinab hospitals (affiliated to the Shiraz University of Medical Sciences) from March 2013 to May 2018.

Results: In this study, 651 twin pregnancies (122 MC and 529 DC) were analyzed. Among MC twin pregnancies, the adverse maternal and neonatal outcomes were similar between the ART and the spontaneous pregnancies, except for lower 1-minute and 5-minute Apgar scores (5.3 vs. 7.2; $P = 0.036$ and 6.4 vs. 8.5; $P = 0.039$, respectively) and a higher fetal death rate in ART group (19% vs. 3.5%, $P = 0.001$). Among the DC twin pregnancies, the risks for pregnancy-related hypertensive disorders, gestational diabetes mellitus, emergency cesarean section and antenatal corticosteroid exposure significantly increased in the ART group ($P < 0.001$, $P = 0.002$, $P = 0.014$, and $P = 0.001$, respectively). Furthermore, DC twins showed significantly higher rates of deliveries before the 34 weeks of gestation (44.8% vs. 31.0%, $P = 0.002$), extremely low birth weight (11.9% vs. 4.0%, $P < 0.001$), intrauterine fetal growth restriction (29.3% vs. 13.5%, $P < 0.001$), lower 1-minute ($P = 0.009$ for fetus A and $P = 0.003$ for fetus B, respectively) and 5-minute ($P < 0.001$ for fetus A and $P < 0.001$ for fetus B, respectively) Apgar scores, perinatal mortality (14.4% vs. 6.9%, $P < 0.001$) and congenital anomaly (8.3% vs. 2.3%, $P = 0.001$) after ART treatment. These results were confirmed by multivariate analysis after adjusting for the baseline variables.

Conclusions: Despite the controversial perinatal outcomes in the literature, we found that ART is associated with an increased risk of perinatal morbidity and mortality, particularly in DC twin pregnancies. Therefore, ART twin pregnancies management requires closer surveillance and advanced facilities at tertiary care centers.

Keywords: Maternal Outcome, Neonatal Outcome, Assisted Reproductive Technology, Monochorionic, Dichorionic

1. Background

Assisted reproductive technology (ART) has been used to treat infertility since its introduction in 1978. Above 20% of ART-related pregnancies are associated with more than one fetus (1). Owing to the high cost of ART and the desire for multiple births, women using fertility treatments might request more than a single embryo to be transferred in the hope to achieve higher live births (1-3). In this regard, increased rate of twin pregnancies has remained an obstacle in ART treatment (4).

Previous studies on comparison of the adverse maternal and neonatal outcomes of twin pregnancies after ART with the non-ART group reported controversial results. Some previous studies reported a higher incidence of perinatal complications of ART twins (5-9), while the others mentioned similar perinatal outcomes or even better outcomes in the ART group (3, 10-13). Therefore, it is impossible to determine perinatal and neonatal outcomes of ART twins by personal judgments or deductions.

2. Objectives

The aim of the current study was to evaluate the effect of ART as part of infertility treatment in the maternal and neonatal outcomes of twin gestations.

3. Methods

This retrospective cohort study was conducted on the women with twin pregnancies who delivered at Hafez and Hazrat Zeinab Hospitals from 1 March 2013 to 31 May 2018. The current study was granted by the Institutional Review Boards of the Shiraz University of Medical Sciences (grant No. of 17286) and approved by the related Ethics Committee (IR.SUMS.REC.1397.366).

ART twin pregnancies conceived following in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) were included in the case group; while the spontaneously conceived twin pregnancies were considered to be the control group.

The exclusion criteria were any history of serious pre-existing chronic diseases, pregnancies conceived after ovulation induction or intrauterine insemination, selective fetal reduction, pregnancies with vanishing embryos, twin-twin transfusion syndrome, uncertain chorionicity, pregnancies with major fetal malformation and fetal loss before 20 weeks of gestation.

Gestational diabetes mellitus (GDM) was confirmed in a previously non-diabetic woman with a 3-hour 100 g oral glucose tolerance test. Gestational hypertension is a condition characterized as persistent blood pressure higher than 140/90 mmHg with no evidence of preeclampsia on at least two occasions after 20 weeks of gestation in a previously normotensive patient. The presence of proteinuria (Dipstick proteinuria of $\geq 1+$ or > 0.3 g/24 hours) or end-organ damage is necessary for the diagnosis of preeclampsia. Abnormal amniotic fluid refers to at least one fetus with polyhydramnios (deepest vertical pocket > 8 cm) or oligohydramnios (deepest vertical pocket < 2 cm). Intrauterine fetal growth restriction (IUGR) is defined as fetal weight below the 10th percentile for gestational age using twin reference curve (14).

Statistical analysis was performed using Statistical Package for the Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). Chi-square test and Fisher's exact test were used to analyze the differences between the categorical variables. The independent sample *t*-test or Mann-Whitney test was used to analyze the differences between continuous variables. *P* values less than 0.05 were considered to be statistically significant.

4. Results

This study included 202 ART-conceived twin pregnancies and 449 spontaneous conceived twin pregnancies. Maternal variables of ART-conceived and spontaneous groups are shown in Table 1. For all dichorionic (DC) twin pregnancies, mean maternal age and the rate of nulliparity were significantly higher in the ART group in comparison to the spontaneous twin group. The body mass index (BMI) was similar in both groups. The hospitalization length was longer for DC mothers in the ART group compared to the control group (5.9; 3 vs. 4.1; 3, $P = 0.002$). Maternal complications such as hypertensive disorders (30.9% vs. 13.8%, $P < 0.001$) and GDM (9.9% vs. 3.4%, $P = 0.002$) were significantly higher in ART DC pregnancies compared to their non-ART counterparts. In addition, the rate of emergency C/S was significantly higher in the ART DC group than the spontaneous group (67.4% vs. 56.3%, $P = 0.014$). Other maternal complications did not show a statistically significant difference between the two groups. Our results also suggested that DC twin mothers in the ART group took more Betamethasone injections (41.4% vs. 27.6%, $P = 0.001$) significantly delivered more early preterm (≤ 34 weeks of gestation) compared to the non-ART DC mothers ($P = 0.002$). The rate of term delivery (≥ 37 weeks of gestation) was significantly higher in the control group in comparison to the ART DC group (29.3% vs. 42%, $P = 0.004$).

Fetal and neonatal variables are listed in Table 2, according to the chorionicity. Intrauterine fetal demise (IUFD) was significantly more common in DC and monochorionic (MC) twins in the ART group (7.2% vs. 2.7%; $P = 0.001$ and 19% vs. 3.5%; $P = 0.001$, respectively). In this study, we found that the ART DC group is more likely to develop IUGR (29.3% vs. 13.5%, $P < 0.001$) and subsequently, birth weight of larger and smaller twins of DC neonates group were significantly lower in the ART group than the control one (2147 ± 705.1 vs. 2359.5 ± 586.3 , $P < 0.001$) and (1811.6 ± 693.1 vs. 2058.8 ± 564.5 , $P < 0.001$). In addition, the rate of extremely low birth weight newborns was significantly higher in the ART DC group (11.9% vs. 4%, $P < 0.001$). Also, 1-minute and 5-minute APGAR scores of first-born twins were significantly lower in the ART DC group in comparison to non-ART DC group (7.7 ± 2.4 vs. 8.3 ± 1.7 ; $P = 0.009$ and 8.9 ± 2.4 vs. 9.5 ± 1.5 ; $P = 0.003$, respectively). Also, we found a significant difference in terms of 1-minute and 5-minute APGAR scores of second-born twin between the ART DC and spontaneous DC groups (7.1 ± 2.8 vs. 7.9 ± 2.2 ; $P < 0.001$ and 8.3 ± 3.0 vs. 9.1 ± 2.1 ; $P < 0.001$, respectively). Only the second-born twin in the ART MC group had lower 1-minute (5.3 ± 3.6 vs. 7.2 ± 2.6 , $P = 0.036$) and 5-minute (6.4 ± 4.3 vs.

Table 1. Maternal Complications of the Studied Groups^a

Maternal Variables	DC Twin Pregnancies, N = 529			MC Twin Pregnancies, N = 122		
	ART, N = 181	SC, N = 348	P Value	ART, N = 21	SC, N = 101	P Value
Maternal age, y	31.8 ± 5.8	28.5 ± 5.3	< 0.001	30.5 ± 4.6	28.2 ± 5.3	0.05
Maternal BMI, kg/m ²	26.4 ± 2.3	26.3 ± 1.4	0.537	26 ± 3.3	25.1 ± 2.7	0.2
Nulliparity	139 (76.8)	139 (39.9)	< 0.001	13 (61.9)	46 (45.5)	0.172
Maternal length of hospital stay, days (mean; median)	5.9; 3	4.1; 3	0.002	7; 4	6.3; 4	0.716
Hypertensive disorders	56 (30.9)	48 (13.8)	< 0.001	3 (14.3)	14 (13.9)	1
GDM	18 (9.9)	12 (3.4)	0.002	3 (14.3)	10 (9.9)	0.696
Emergency C-section	122 (67.4)	196 (56.3)	0.014	12 (57.1)	67 (66.3)	0.422
Oligohydraminos	9 (5)	10 (2.9)	0.218	0 (0.0)	6 (5.9)	0.588
Polyhydraminos	3 (1.7)	3 (0.9)	0.416	0 (0.0)	0 (0.0)	-
Placental abruption	7 (3.9)	12 (3.4)	0.806	2 (9.5)	5 (5.0)	0.346
PPROM	38 (21.0)	67 (19.3)	0.634	2 (9.5)	16 (15.8)	0.736
Preterm labor	74 (40.9)	118 (33.9)	0.113	8 (38.1)	36 (35.6)	0.831
Antenatal corticosteroids	75 (41.4)	96 (27.6)	0.001	10 (47.6)	36 (35.6)	0.303
Cervical cerclage	2 (1.1)	4 (1.1)	1	0 (0.0)	1 (1.0)	1
GA at delivery, weeks	33.9 ± 3.9	35.1 ± 3.2	<0.001	32.4 ± 4.2	33.3 ± 3.7	0.362
GA at delivery ≤ 34 weeks	81 (44.8)	108 (31.0)	0.002	13 (61.9)	56 (55.4)	0.587

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; DC, dichorionic; GA, gestational age; GDM, gestational diabetes mellitus; MC, monochorionic; PPROM, preterm premature rupture of membranes; SC, spontaneous conception.

^aValues are expressed as mean ± SD or No. (%) unless otherwise indicated.

8.5 ± 2.5, P = 0.039) APGAR scores after birth in comparison to the spontaneous MC group. Also, congenital anomalies were more common in the smaller newborns of the ART DC group than in the spontaneous DC group (8.3% vs. 2.3%, P = 0.001). The rate of neonatal death was significantly higher in the ART DC group in comparison to the spontaneous DC group (7.2% vs. 4.2%, P = 0.036). Height (43.6 ± 6.5 vs. 45.5 ± 4.9, P < 0.001) and head circumference (31.2 ± 4.1 vs. 32.3 ± 2.7, P < 0.001) of neonates were significantly lower in the ART DC group compared with non-ART DC group. Although the rate of NICU admission was similar in study and control groups, length of stay in NICU was longer in the ART DC group in comparison to the spontaneous DC group (10.5; 8 vs. 9.0; 6, P = 0.007). Respiratory distress syndrome (RDS) was a prevalent complication in the ART DC group in comparison to the spontaneous DC group (30.7% vs. 21.8%, P = 0.002).

The differences between the ART and spontaneous groups after adjustment for maternal age, BMI, and parity were statistically significant (Table 3), except for the incidence of RDS in the DC twins (AOR = 1.3 (0.9 - 1.8)).

5. Discussion

The current study showed the effect of ART treatment on maternal and neonatal outcomes of twin pregnancies. Moreover, ART DC twins are at greater risk of very low birth weight, extremely low birth weight, very preterm birth, IUGR, RDS, lower 1-minute and 5-minute APGAR scores, and congenital anomalies. The incidence of the maternal complications was not significantly different for MC twins in both ART and spontaneous conceived groups, which might be due to the small sample size of MC twin pregnancies. In ART-conceived pregnancies, we found that ART mothers tend to be older and had higher rates of hypertensive disorders, GDM, emergent C/S and antenatal corticosteroid exposure compared to the non-ART mothers.

Previous studies have shown that MC twin pregnancies are associated with higher perinatal morbidity and mortality (15, 16). In the current study, we found that ART MC twin pregnancies are expected to have obstetrical and neonatal outcomes that are similar to the spontaneous MC twin pregnancies; except for the rate of fetal death, which was 5.4-fold more prevalent in the ART MC group. On the other hand, Sun et al. (17) reported a similar perinatal outcome of the MC twins after ART treatment compared to the non-

Table 2. Neonatal Complications of the Studied Groups^a

Neonatal Variables	DC Twins, N = 1058			MC Twins, N = 244		
	ART, N = 362	SC, N = 696	P Value	ART, N = 42	SC, N = 202	P Value
LBW	186 (51.4)	375 (53.9)	0.44	21 (50)	117 (57.9)	0.346
Very LBW	44 (12.2)	59 (8.5)	0.056	9 (21.4)	32 (15.8)	0.378
Extremely LBW	43 (11.9)	28 (4)	< 0.001	7 (16.7)	24 (11.9)	0.397
IUGR	53 (29.3)	47 (13.5)	< 0.001	6 (28.6)	32 (31.7)	0.779
Height, cm	43.6 ± 6.5	45.5 ± 4.9	< 0.001	42.2 ± 6.1	42.8 ± 6.1	0.493
Head circumference, cm	31.2 ± 4.1	32.3 ± 2.7	< 0.001	30.4 ± 3.9	30.7 ± 3.8	0.471
RDS	111 (30.7)	152 (21.8)	0.002	11 (26.2)	67 (33.2)	0.378
1-min APGAR score first-born	7.7 ± 2.4	8.3 ± 1.7	0.009	6.5 ± 3.4	7.6 ± 2.1	0.155
APGAR 1 min < 7	32 (17.7)	33 (9.5)	0.006	7 (33.3)	17 (16.8)	0.127
5-min APGAR score first-born	8.9 ± 2.4	9.5 ± 1.5	0.003	7.7 ± 3.9	8.9 ± 2.0	0.176
APGAR 5 min < 7	14 (7.7)	12 (3.4)	0.03	4 (19)	8 (7.9)	0.218
1-min APGAR score second-born twin	7.1 ± 2.8	7.9 ± 2.2	< 0.001	5.3 ± 3.6	7.2 ± 2.6	0.036
APGAR 1 min < 7	46 (25.4)	51 (14.7)	0.002	10 (47.6)	23 (22.8)	0.02
5-min APGAR score second-born twin	8.3 ± 3.0	9.1 ± 2.1	< 0.001	6.4 ± 4.3	8.5 ± 2.5	0.039
APGAR 5 min < 7	23 (12.7)	23 (6.6)	0.018	6 (28.6)	12 (11.9)	0.084
Mortality						
Intrauterine fetal death	26 (7.2)	19 (2.7)	0.001	8 (19)	7 (3.5)	0.001
Neonatal death	26 (7.2)	29 (4.2)	0.036	2 (4.8)	21 (10.4)	0.385
Perinatal mortality	52 (14.4)	48 (6.9)	< 0.001	10 (23.8)	28 (13.9)	0.106
Hyperbilirubinemia	63 (17.4)	94 (13.5)	0.091	8 (19)	24 (11.9)	0.211
Congenital anomaly						
Anomalies of a larger baby	9 (5)	8 (2.3)	0.098	0 (0.0)	5 (5.0)	0.586
Anomalies of a smaller baby	15 (8.3)	8 (2.3)	0.001	1 (4.8)	2 (2.0)	0.436
Admissions to NICU	141 (39)	301 (43.2)	0.179	17 (40.5)	109 (54.0)	0.112
Length of stay in NICU, days (mean, median)	10.5; 8	9.0; 6	0.007	10.2; 9	10.6; 7	0.132

Abbreviations: ART, assisted reproductive technology; DC, dichorionic; IUGR, intrauterine fetal growth restriction; LBW, low birth weight; MC, monochorionic; RDS, respiratory distress syndrome; SC, spontaneous conception.

^aValues are expressed as mean ± SD or No. (%) unless otherwise indicated.

ART MC twins.

In line with other studies (6, 18-20), pregnancy-related hypertensive disorders (preeclampsia and gestational hypertension) occurred more frequently in DC twin pregnancies after ART treatment. A possible reason for the increased risk of hypertensive disorders could be the presence of elderly nulliparous women in the ART group. Conversely, Caserta et al. (8) and Fan et al. (21) found similar rates of hypertensive disorders in the ART and spontaneous groups.

In DC pregnancies, GDM was significantly more prevalent in the ART group compared to the non-ART group, which is consistent with a previous study reporting a

higher incidence of GDM with ART treatment (20); however, other studies did not mention this association (5, 18). A number of studies have suggested that progesterone use during pregnancy, previous ovarian hyper-stimulation syndrome (OHSS), and history of polycystic ovary syndrome (PCOS) could be associated with increased risk of GDM developing in ART-conceived pregnancies (22, 23). In the current study, patients with PCOS were excluded; therefore, it cannot explain the increased risk of GDM in ART-conceived twin pregnancies. Wang et al. (24) reported the advanced maternal age and preconception obesity as the main risk factors for developing GDM in ART-conceived pregnancies.

Table 3. Multivariate Analysis of Maternal and Neonatal Outcomes of the Studied Groups Adjusted for Maternal Age, Parity, and Body Mass Index

Study Groups/Complication	Adjusted OR	95% CI	P Value
MC twin			
Intrauterine fetal death	6.6	2.2 - 19.3	0.001
1-min APGAR score fetus B < 7	3.3	1.2 - 9.3	0.026
DC twin			
Hypertensive disorders	2.1	1.2 - 3.5	0.007
GDM	3.3	1.4 - 7.9	0.008
Emergency C/S	1.6	1.0 - 2.5	0.036
GA at delivery \leq 34 weeks	1.7	1.1 - 2.7	0.015
Extremely LBW	3.9	2.2 - 7.1	< 0.001
IUGR	2.1	1.2 - 3.5	0.007
RDS	1.3	0.9 - 1.8	0.158
1-min APGAR score fetus A < 7	2.1	1.1 - 3.9	0.020
5-min APGAR score fetus A < 7	4.3	1.8 - 10.4	0.001
1-min APGAR score fetus B < 7	2.3	1.3 - 3.9	0.004
5-min APGAR score fetus B < 7	2.7	1.3 - 5.5	0.009
Intrauterine fetal death	2.7	1.3 - 5.7	0.007
Neonatal death	2.0	1.1 - 3.7	0.031
Perinatal death	2.1	1.3 - 3.5	0.003
Congenital anomaly smaller baby	5.2	1.8 - 15.1	0.002

Abbreviations: DC, dichorionic; GDM, gestational diabetes mellitus; IUGR, intrauterine fetal growth restriction; MC, monochorionic; RDS, respiratory distress syndrome.

A study by Andrijasevic et al. discovered that ART treatment does not have a negative impact on outcomes of twin pregnancies, except for higher rates of premature rupture of membranes (PROM) and C/S (25). However, the results of the current study do not suggest any significant difference in terms of preterm premature rupture of membranes (PPROM) rate in the ART and spontaneous groups.

In contrary to the findings of Moini et al. (5), an increase was observed in the rate of emergency C/S in ART patients, which could be probably due to the increased rate of emergency C/S such as a higher prevalence of pregnancy-induced complications and lower thresholds for caesarean delivery among the ART mothers.

In our study, the perinatal mortality rate was 2.1-fold higher in the ART DC twins compared to the non-ART group, which seems to be associated with higher rates of IUFD, prematurity and RDS in the ART twins. This finding is consistent with some previous studies (5, 7), while other studies did not report such an increased risk (3, 18). Some studies have shown a lower rate of perinatal mortality for ART twin pregnancies (26, 27), which might be due to the differences in the ART pregnancy management protocols

implemented in clinical practice.

The increase in neonatal complications such as extremely low birth weight (< 1000 g), very preterm birth (\leq 34 weeks of gestation), and lower APGAR scores in ART twins were inconsistent with the findings of previous studies (11, 12). The mean body weight, height and head circumference at birth were lower in the ART twins. In our study, the significant differences in anthropometric characteristics of ART and non-ART twins could be attributed to the increased rate of IUGR in the ART group. However, most of the previous studies did not support such an association between IUGR and ART treatment (3, 5, 8).

In the present study, the congenital anomaly was another studied variable. In the smaller newborns of the ART DC group, congenital anomalies were 3.6-fold more prevalent compared to the non-ART group, which is in line with the study of Kuwata et al. (28); however, other studies did not report such association (3, 11).

The major strength of this study resides in the fact that our study is one of the few studies addressing both MC and DC pregnancies. The other point is that all pregnancies were managed by one group of perinatologists following

the same instructions. However, there were some limitations among which, lack of information about the underlying causes of infertility and the retrospective nature of the study can be mentioned. This study could not be considered a suitable representative model for all Iranian women with twin pregnancies due to the selection bias regarding the particular nature of tertiary referral centers.

During a preconception visit, couples have the right to be fully informed regarding the maternal and neonatal adverse outcomes of ART treatment in order to help them through the decision making process. Moreover, embryo reduction techniques should be considered in high-risk ART-conceived twin pregnancies during the first and early second trimester.

Monitoring and delivery of ART twin pregnancies should be performed at tertiary care centers where advanced fetal surveillance and NICU services are accessible. Furthermore, a team approach with obstetricians and neonatologists is essential to improve both the maternal and neonatal outcomes.

5.1. Conclusions

In conclusion, the result of our study is not consistent with previous studies (10-13) reporting similar perinatal outcomes between ART and non-ART twin pregnancies. We found that ART is associated with the higher risk of pregnancy-related hypertensive disorders, GDM, emergency C/S, very preterm birth, very low birth weight, extremely low birth weight, and longer NICU hospitalization in the DC twin pregnancies as well as the higher rate of IUFD and lower APGAR scores in the MC twins in comparison to the spontaneous twin pregnancies.

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Footnotes

Authors' Contribution: Study concept and design: Kamran Hessami. Analysis and interpretation of data: Samaneh Moghaddamzadeh Shoushtari, and Anahita Hessami. Critical revision: Maryam Kasraeian. Statistical Analysis: Kamran Hessami and Anahita Hessami.

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