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Obstetric and neonatal outcomes of twin pregnancies conceived by assisted reproductive technology compared with twin pregnancies conceived spontaneously: a prospective follow-up study

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ABSTRACT

Objective: To compare the obstetric and neonatal outcomes of twin pregnancies conceived by assisted reproduction technology (ART) with spontaneously conceived (SC) twin pregnancies.
Study design: A prospective cohort study compared all dichorionic twin pregnancies in nulliparous women following fresh in vitro fertilization/intra-cytoplasmic sperm injection (ICSI) or ICSI cycles at Royan Institute (n = 320) with SC dichorionic twin pregnancies in nulliparous women at Arash Women's hospital (n = 170) from January 2008 to October 2010. These pregnancies were followed-up until hospital discharge following delivery. Obstetric and neonatal outcomes of SC and ART twin pregnancies were compared.
Results: Multivariate analysis, adjusted for maternal age and body mass index, revealed that the obstetric outcomes were similar in both groups. However, the risks of very preterm birth [odds ratio (OR) 5.2, 95% confidence interval (CI) 2.1–12.9], extremely low birth weight (OR 2.2, 95% CI 1.0–3.9), admission to a neonatal intensive care unit (OR 2.0, 95% CI 1.2–3.2) and perinatal mortality (OR 2.3, 95% CI 1.2–4.0) were higher in the ART group.
Conclusions: The maternal outcomes of ART dichorionic twins were comparable with those of SC twins. However, despite the same obstetric management, the rates of very preterm birth, extremely low birth weight, admission to a neonatal intensive care unit and perinatal mortality were significantly higher in the ART group.

1. Introduction

Twin pregnancies following assisted reproductive technology (ART) have increased worldwide in recent years because of increased requests for ART and the transfer of two or three embryos to achieve a higher pregnancy rate. This is despite endeavours aimed at limiting the incidence of multiple pregnancies after ART (e.g. single embryo transfer). The transfer of two or more embryos in relatively young women is particularly common where in vitro fertilization (IVF) treatments are quite expensive and couples wish to maximize their chance of achieving a pregnancy [1]. However, there is some evidence showing that ART singletons are at greater risk of preterm birth, low birth weight and decreased fetal growth than spontaneously conceived (SC) singletons [2–4]. Concerning twin pregnancies, studies comparing maternal and neonatal outcomes of ART and SC twin pregnancies have reported conflicting results. Some studies reported that perinatal complications such as gestational diabetes mellitus [5,6] and preterm delivery [5–13] were significantly more common in ART twins [14]; in contrast, some studies obtained similar perinatal outcomes for ART and SC twins [1,15–30]. In terms of neonatal outcomes, some studies have shown that low birth weight [5–7,9,12,13,21], weight discordance between twins [12,21,31], admission to a neonatal intensive care unit (NICU) and number of bedridden days in hospital [8–10,13] were worse in ART twins. Other studies did not accept these findings, and reported that ART twins had similar neonatal outcomes compared with SC twins [15,32–35]. However, some reports have suggested better perinatal outcomes after IVF [34,36,37]. Accordingly, there are conflicting data concerning perinatal and neonatal outcomes of twins in ART pregnancies, which may be due to differences in the study population, management methods of twin pregnancies, and

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whether or not monochorionicity was considered as a risk factor for poor prenatal outcomes. The present study could not use a single group of doctors to manage all pregnancies as the study population was gathered from two centres. To avoid any possible bias deriving from differences in obstetric management, all pregnancies were managed by the same limited group of doctors using the same obstetric protocols. The aim of this prospective study was to evaluate and compare obstetric and neonatal outcomes of ART and SC twin pregnancies.

2. Materials and methods

This prospective cohort study was performed at Royan Institute and Arash Women's Hospital in Iran from January 2008 to October 2010. The Institutional Review Boards and the Ethical Committees of Royan Institute and Tehran University of Medical Science approved this study.

The ART pregnancies were dichorionic, diamniotic twin pregnancies following fresh IVF/intra-cytoplasmic sperm injection (ICSI) or ICSI cycles at Royan Institute. Those women who had twin pregnancies following infertility treatment due to polycystic ovarian syndrome and uterine factor, and those who had experienced ovarian hyperstimulation syndrome during the controlled ovarian hyperstimulation protocols were excluded. The SC pregnancies were dichorionic, diamniotic twin pregnancies referred to Arash Women's Hospital, which is affiliated to Tehran University of Medical Science. All the women with history of medical diseases and surgery on pelvic organs; height <150 cm; smokers; non-Iranian race; pregnancies conceived by ovulation induction, intrauterine injection (IUI) and selective fetal reduction; and pregnancies with vanishing embryos were excluded from the study.

The women in both groups were nulliparae and were included following the observation of two gestational sacs on vaginal sonography at the first trimester. All scans were performed by one radiologist at one referral centre. These women were followed-up until hospital discharge following delivery. Only those patients referred to the study centres before 14 weeks of gestation and delivering after 22 weeks of gestation were included in this study. After accurate selection, the study included 400 twin pregnancies: 230 were conceived by IVF/ICSI and 170 were SC. These pregnancies were managed by two groups of obstetricians following the same protocol. Information about the obstetric and neonatal outcomes of the two groups was obtained from the patients' files, telephone calls, hospital records and through questionnaires completed by a responsible obstetrician. All the women underwent prenatal care at the Department of Obstetrics and Gynaecology at Royan Institute, and delivered at a university-based hospital for high-risk maternal-fetal medicine.

Data on maternal and neonatal outcomes were collected using a two-part questionnaire. The first part was related to demographic data such as maternal age, educational level, body mass index (BMI), pregnancy and maternal history, parity, type of conception, type of infertility and duration of infertility. The second part dealt with pregnancy outcomes such as maternal complications [premature rupture of membranes (rupture of membranes before 37 weeks of gestation), preterm delivery (between 24 and 36 weeks or before 37 weeks of gestation), very preterm delivery (before 32 weeks of gestation), gestational diabetes mellitus, pre-eclampsia, renal infection, amniotic fluid disorders, placenta previa, placenta abruption, abnormal haemorrhage] and fetal–neonatal complications (intrauterine fetal death before 22 weeks of gestation, low birth weight, detectable anomalies, neonatal mortality). Maternal demographics, antepartum complications, mode of delivery and perinatal outcomes were compared between the two groups.

Gestational diabetes mellitus was diagnosed based on a 3-h 100-g oral glucose tolerance test. Pregnancy-induced hypertension was defined as persistent blood pressure ≥140/90 mmHg after 20 weeks of gestation in previously normotensive women. Pre-eclampsia was diagnosed when pregnancy-induced hypertension was associated with proteinuria ≥100 mg/dl by urine analysis or ≥300 mg/24 h. Gestational age was calculated from the date of embryo transfer (+2 weeks) for the ART pregnancies, and from the date of the last menstrual period, confirmed by the first trimester ultrasound estimation before 14 weeks of pregnancy, for the SC pregnancies. Chorionicity was determined during the same ultrasound examination on the basis of the number of placentae, lambda and T sign, and intertwin membrane thickness [38]. Intrauterine growth retardation was diagnosed when growth was below the third percentile for gestational age, and discordant growth between twins was defined as a birthweight difference of more than 25% between the twins [38]. Perinatal mortality was calculated by dividing the number of stillbirths of babies ≥22 weeks and weighing more than 500 g plus the number of liveborn neonates who died within 7 days of delivery by the total number of births [38].

Data are presented as means ± standard deviation of the mean, proportions and odds ratios. Statistical analysis was performed using Statistical Package for the Social Sciences Version 16.0.0 (SPSS Inc., Chicago, IL, USA) and Stata Version 9 (Stata Corp., College Station, TX, USA). The obtained data were analysed using unpaired Student's *t*-test for continuous variables, and Chi-squared test or Fisher's exact test for categorical variables. Multiple logistic regression was used to assess the association between pregnancy outcomes and the study groups, adjusting for potential confounding variables including maternal age and BMI. A two-tailed *p*-value <0.05 was used to indicate statistical significance.

3. Results

Maternal characteristics of the two groups were compared (Table 1). As expected, mean maternal age was significantly higher

Table 1
Clinical features of the study population.

	Twins conceived spontaneously (n = 170)	Twins conceived by ART (n = 230)	p-value
Maternal age (years)[a]	27.3 ± 5.1	30.6 ± 4.3	0.001[c]
Body mass index (kg/m^2)[a]	28.2 ± 3.6	28.4 ± 3.9	0.8
Duration of pregnancy (weeks) (mean ± SD)[a]	35.2 ± 2.0	34.5 ± 2.5	0.005[c]
Caesarean section[b]	151(88.8)	214 (93.4)	0.1

ART, assisted reproductive technology; SD, standard deviation.
[a] Student's *t*-test.
[b] Chi-squared test.
[c] Significant difference.

Table 2
Maternal complications in the study population.

Outcome	Twins conceived spontaneously (n = 170)	Twins conceived by ART (n = 230)	p-value[a]
Gestational diabetes	15 (8.8)	21 (9.1)	0.9
Hypertensive disorder	18 (10.5)	30 (13)	0.7
Placental abruption	2 (1.1)	5 (2.1)	0.55
Oligohydramnion	1 (0.5)	3 (1.3)	0.6
Polyhydramnion	1 (0.5)	2 (0.8)	0.9
Postpartum bleeding	10 (5.8)	16 (6.9)	0.67
Delivery at 32–36 weeks	78 (45.8)	83 (36)	0.048
Delivery at 30–31 weeks	5 (2.9)	25 (10.8)	0.003
Delivery before/at 29 weeks	2 (1.1)	10 (4.3)	0.066
Premature rupture of membranes	31 (18.2)	46 (20)	0.75

ART, assisted reproductive technology.
[a] Chi-squared test.