


Perinatal outcome of monochorionic and dichorionic twins after spontaneous and assisted conception: a retrospective cohort study

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Key words

Assisted conception, chorionicity, monochorionic, perinatal outcome, spontaneous, twins

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Conflict of interest

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Abstract

Introduction. The aim of this study was to compare pregnancy outcomes in twin pregnancies after assisted conception and spontaneous conception, according to chorionicity. **Material and methods.** Retrospective cohort study of 1305 twin pregnancies between 1995 and 2015. All spontaneous ($n = 731$) and assisted conception conceived ($n = 574$) twin pregnancies with antenatal care and delivery in University Medical Center Utrecht, the Netherlands, a tertiary obstetric care center were studied according to chorionicity. **Results.** Maternal age and incidence of nulliparity were higher among the assisted conception twins. Hypertensive disorders also appeared to be more frequent in assisted conception pregnancies, which could largely be explained by the higher proportion of elderly nulliparous women in this group. Spontaneously conceived twins were born earlier than twins after assisted conception, with subsequent lower birthweights and more admissions to a neonatal intensive care unit with increased neonatal morbidity. Monochorionic twins had worse pregnancy outcomes compared with dichorionic twins, irrespective of mode of conception; monochorionic twins conceived by assisted reproduction had more neonatal morbidity (mainly respiratory distress syndrome and necrotizing enterocolitis) and late neonatal deaths compared with spontaneously conceived monochorionic twins. **Conclusions.** Spontaneously conceived twins have worse pregnancy outcome compared with twins after assisted conception, probably due to a lower incidence of monochorionicity in the assisted conception group. The already increased perinatal risks in monochorionic twins are even higher in monochorionic twins conceived after infertility treatments compared with spontaneously conceived monochorionic twins, which warrants extra attention to these high-risk pregnancies.

Abbreviations: AC, assisted conception; DC, dichorionic; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; MC, monochorionic; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome.

Introduction

Assisted reproductive technology has become a routine and successful treatment for subfertility. It is well recognized that assisted conception (AC) significantly increases the risk of multiple gestations. Many studies regarding outcome in AC pregnancies have shown that singleton pregnancies obtained by AC are associated with poorer obstetric and neonatal outcome in comparison with naturally conceived singletons, even after matching for maternal age and parity (1–3).

Findings from various studies on perinatal outcome in AC-conceived twin pregnancies compared with spontaneously conceived twin pregnancies, however, have been inconsistent. In the majority of these studies chorionicity had not been taken into account. Monochorionic (MC) placentation with a relatively poor perinatal outcome occurs less frequently in AC pregnancies. It is therefore hypothesized that twins after infertility treatment should have better outcomes than spontaneously conceived twins. It is not yet clear, however, whether twin pregnancies after AC must be considered at higher obstetrical risk than spontaneously conceived ones.

The purpose of this study was to compare obstetric and perinatal outcomes of MC and dichorionic (DC) twin pregnancies by mode of conception.

Material and methods

The medical records of all patients with twin pregnancies who had their antenatal care and delivery in the University Medical Center Utrecht, a tertiary referral center, were reviewed for the period January 1995 until December 2015. All twin pregnancies were retrieved from the electronic data bases.

Exclusion criteria

We excluded all patients with twin pregnancies who were referred during pregnancy, monoamniotic twins, pregnancies with selective feticide or termination of pregnancy and those with birth or fetal death before 20 weeks of gestation and/or birthweight <500 g, as well as pregnancies with major fetal malformations with infaust prognosis. After accurate selection, the study included 1305 twin pregnancies, of which 731 were conceived spontaneously and 574 by AC.

Data collection and local policy

Baseline characteristics, maternal outcome and neonatal outcome were documented according to the mode of conception. AC included various infertility treatments like

in vitro fertilization (IVF), IVF with intracytoplasmic sperm injection (ICSI) and ovulation induction (either by clomifene citrate or follicle-stimulating hormone injections). The majority of the women undergoing AC were treated in our fertility clinic.

Chorionicity was determined on the basis of first-trimester ultrasound assessment of the dividing membrane characteristics and/or routinely postpartum pathological examination of placentas and intertwin membranes.

All twin gestations were monitored according to a standard protocol, which consisted of a first-trimester determination of chorionicity and a detailed anomaly scan at 20 weeks of gestational age; DC twin pregnancies were monitored by regular ultrasound assessment of growth, amniotic fluid volume and Doppler of the umbilical artery at least at 20, 24 and 28 weeks and fortnightly thereafter. In monochorionic twin pregnancies evaluation of growth and Doppler profiles of umbilical artery and middle cerebral artery were performed every 2 weeks from 14 weeks onwards. Women with either nonreassuring fetal findings or with maternal complications were submitted to frequent but at least twice weekly maternal–fetal evaluations that were performed during hospitalization or during visits at the outpatient clinic. In uncomplicated MC twins, elective delivery was offered around 37 weeks of gestation.

Definitions

Gestational age was calculated from the first day of the last menstrual period confirmed by first-trimester ultrasound or from the day of oocyte pick-up in the case of assisted reproduction. Stillbirth was defined as an intrauterine fetal demise of a fetus >500 g and/or ≥ 20 weeks of gestation. Gestational age at time of stillbirth was ascertained by ultrasound. Early neonatal death was defined as death of an infant during the first 7 days of life, whereas late neonatal death was defined as death between 8 and 28 days after birth. Composite major neonatal morbidity was defined as the occurrence of one or more of the following issues: respiratory distress syndrome (RDS) (4), intraventricular hemorrhage (5), necrotizing enterocolitis (NEC) (6) and/or proven sepsis. Low birthweight was defined as neonatal weight <2500 g and

Key message

The already increased perinatal risk in monochorionic twins is even higher in these twins conceived by infertility treatment compared with spontaneous conception.

very low birthweight was defined as neonatal weight <1500 g. Birthweight below the 10th centile for gestational age was considered as “small-for-gestational-age”. Diabetes mellitus was defined as pre-existing diabetes (insulin-dependent and non-insulin-dependent) and gestational diabetes. Diagnosis of hypertension was defined as persistent blood pressure of $\geq 140/90$ mmHg after 20 weeks of gestation in previously normotensive women (pregnancy-induced hypertension) or pre-existing hypertension. Pre-eclampsia was defined as hypertension accompanied by proteinuria of ≥ 300 mg/24 h. Preterm uterine contractions (imminent preterm labor) were

defined as regular uterine contractions with shortening of cervical length or disclosure that required tocolytic intervention. Preterm birth was considered as such when delivery occurred before 37 weeks of gestation, with delivery before 32 weeks defined as very preterm birth. Elective cesarean section was defined as a cesarean section without labor.

Statistical analyses

First, we analyzed obstetric and perinatal outcome according to mode of conception (spontaneous vs.

Table 1. Pregnancy characteristics and outcome of spontaneous and assisted conceived twins, irrespective of chorionicity.

	All twin pregnancies		p-value	OR (95% CI)
	Spontaneous conception (n = 731)	Assisted conception (n = 574)		
Chorionicity; dichorionic placentation	508 (69.4)	545 (94.9)	<0.001	8.3 (6.2–11.0)
Maternal age, years (mean \pm SD)	32.1 \pm 4.7	33.9 \pm 4.3	<0.001	
Age ≥ 35 years, n (%)	229 (31.3)	268 (46.7)	<0.001	1.9 (1.6–2.3)
Parity, n (median, range)	1 (0–8)	0 (0–6)	<0.001	
Nulliparous, n (%)	310 (42.4)	378 (65.9)	<0.001	2.6 (2.2–3.1)
Imminent preterm labor, n (%)	150 (20.5)	130 (22.6)	0.180	
Hypertensive disorders, n (%)	118 (16.2)	116 (20.2)	0.008	1.3 (1.1–1.6)
Pregnancy-induced and pre-existing hypertension, n (%)	44 (6.1)	36 (6.3)	0.836	
Preeclampsia, n (%)	73 (10.0)	83 (14.5)	<0.001	1.5 (1.2–1.9)
Diabetes, n (%)	27 (3.7)	21 (3.7)	0.970	
Cesarean section, n (%)	352 (48.3)	227 (48.7)	0.875	
Elective CS, n (%)	137 (18.8)	109 (19.0)	0.901	
Emergency CS, n (%)	214 (29.5)	168 (29.5)	1.000	
	n = 1462 fetuses	n = 1148 fetuses		
Gestational age, weeks (median, range)	36 ⁺⁶ (20 ⁺² –41 ⁺³)	37 ⁺¹ (22 ⁺⁴ –41 ⁺⁶)	<0.001	
<32 weeks, n (%)	91 (12.4)	40 (7.1)	<0.001	0.5 (0.4–0.7)
32–37 weeks, n (%)	278 (38.0)	210 (36.6)	0.457	
≥ 37 weeks, n (%)	362 (49.6)	324 (56.4)	0.001	1.3 (1.1–1.5)
Birthweight, grams (mean \pm SD)	2410 \pm 665	2458 \pm 632	0.058	
SGA, n (%)	229 (15.7)	179 (15.7)	0.958	
Low birthweight, n (%)	737 (50.4)	550 (47.9)	0.211	
Very low birthweight, n (%)	158 (10.8)	92 (8.0)	0.016	0.7 (0.6–0.9)
Mortality				
IUFD, n (%)	21 (1.4)	5 (0.4)	0.011	0.3 (0.1–0.8)
Early NND, n (%)	27 (1.8)	13 (1.1)	0.141	
Late NND, n (%)	3 (0.2)	3 (0.3)	0.766	
Neonatal morbidity ^a				
RDS, n (%)	104 (7.1)	70 (6.1)	0.304	
IVH, n (%)	36 (2.5)	23 (2.0)	0.435	
NEC, n (%)	14 (1.0)	13 (1.1)	0.657	
Sepsis, n (%)	83 (5.6)	43 (3.7)	0.027	0.7 (0.5–1.0)
Major neonatal morbidity, n (%) ^a	171 (11.7)	108 (9.4)	0.063	
Admission to NICU, n (%) ^a	253 (17.3)	157 (13.7)	0.012	0.8 (0.6–0.9)

Abbreviations: CI, confidence interval; CS, cesarean section; IUFD, intrauterine fetal death; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; OR, odds ratio; RDS, respiratory distress syndrome; SGA, small for gestational age.

^aExcluding intrauterine fetal deaths.

assisted conception). Second, comparisons were made according to chorionicity within the mode of conception groups. And last, outcomes of MC twins conceived by any infertility treatment were compared with their DC counterparts. Statistical analysis was performed with the SPSS statistical package 21.0 (SPSS Inc., Chicago, IL, USA). Chi-squared test was used for analyzing differences between categorical variables. The independent sample *t*-tests or a Mann–Whitney *U*-test were used to analyze differences between continuous variables. Logistic regression was performed and we report odds ratios (OR) with 95% CI. Possible confounders (like maternal age and parity) were corrected for with logistic regression. Values of $p < 0.05$ (two-

sided) were considered to indicate statistically significant differences.

Ethical approval

This study has been reviewed and approved by the Medical Ethics Review Committee of the University Medical Center Utrecht (protocol number 13/308, date of approval: 12 June 2013).

Results

During the study period, 1305 patients with twin pregnancies had their antenatal care and delivery at the

Table 2. Pregnancy characteristics and outcome of spontaneous and assisted conceived dichorionic twins.

	Dichorionic twins		<i>p</i> -value	OR (95% CI)
	Spontaneous conception (<i>n</i> = 508)	Assisted conception (<i>n</i> = 545)		
Maternal age, years (mean ± SD)	32.5 ± 4.5	33.9 ± 4.3	<0.001	
Age ≥35 years, <i>n</i> (%)	176 (34.6)	256 (47.0)	<0.001	2.0 (1.7–2.5)
Parity (median, range)	1 (0–5)	0 (0–6)	<0.001	
Nulliparous, <i>n</i> (%)	214 (42.1)	355 (65.1)	<0.001	3.1 (2.5–3.7)
Imminent preterm labor, <i>n</i> (%)	108 (21.3)	126 (23.1)	0.305	
Hypertensive disorders, <i>n</i> (%)	87 (17.2)	109 (20.0)	0.102	
Pregnancy-induced and pre-existing hypertension, <i>n</i> (%)	27 (5.4)	33 (6.1)	0.527	
Preeclampsia, <i>n</i> (%)	56 (11.0)	79 (14.5)	0.017	1.4 (1.1–1.8)
Diabetes, <i>n</i> (%)	22 (4.3)	18 (3.3)	0.218	
Cesarean section, <i>n</i> (%)	247 (48.9)	261 (48.3)		
Elective CS	89 (17.5)	102 (18.8)	0.793	
Emergency CS	158 (31.3)	159 (29.4)	0.444	
	<i>n</i> = 1016 fetuses	<i>n</i> = 1090 fetuses		
Gestational age, weeks (median, range)	37 ⁺¹ (23 ⁺² –41 ⁺³)	37 ⁺² (22 ⁺⁴ –41 ⁺⁶)	0.149	
<32 weeks, <i>n</i> (%)	122 (12.0)	73 (6.7)	<0.001	0.4 (0.3–0.7)
32–37 weeks, <i>n</i> (%)	344 (33.9)	394 (36.1)	0.271	
≥37 weeks, <i>n</i> (%)	550 (54.1)	622 (57.2)	0.163	
Birthweight, grams (mean ± SD)	2471 ± 679	2475 ± 625	0.901	
SGA, <i>n</i> (%)	166 (16.5)	169 (16.5)	0.584	
Low birthweight, <i>n</i> (%)	462 (45.5)	510 (46.8)	0.545	
Very low birthweight, <i>n</i> (%)	105 (10.3)	81 (7.4)	0.019	0.7 (0.5–0.9)
Mortality				
IUFD, <i>n</i> (%)	10 (1.0)	14 (0.7)	0.082	
Early NND, <i>n</i> (%)	16 (1.6)	13 (1.2)	0.452	
Late NND, <i>n</i> (%)	3 (0.3)	1 (0.1)	0.284	
Neonatal morbidity ^a				
RDS, <i>n</i> (%)	69 (6.8)	59 (5.4)	0.186	
IVH, <i>n</i> (%)	23 (2.3)	21 (1.9)	0.589	
NEC, <i>n</i> (%)	6 (0.6)	8 (0.7)	0.683	
Sepsis, <i>n</i> (%)	46 (4.5)	40 (3.7)	0.320	
Major neonatal morbidity, <i>n</i> (%) ^a	107 (10.5)	94 (8.6)	0.140	
Admission to NICU, <i>n</i> (%) ^a	151 (14.9)	141 (12.9)	0.201	

Abbreviations: CI, confidence interval; CS, cesarean section; IUFD, intrauterine fetal death; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; OR, odds ratio; RDS, respiratory distress syndrome; SGA, small for gestational age.

^aExcluding intrauterine fetal deaths.

department of Obstetrics of the University Medical Center Utrecht, the Netherlands. Of these, 574 pregnancies had been conceived by AC, of whom 71 had been conceived by intrauterine insemination, 56 after ovulation induction and 447 by IVF/ICSI. There were 1053 DC twins and 252 MC twins. Only 29 MC twins were conceived by AC, of which 23 were conceived by IVF/ICSI. In this data set, MC twins comprise 5% of all twins after AC.

Table 1 shows the comparison of pregnancy characteristics and outcomes of spontaneously conceived twins and twins conceived by assisted reproduction. Maternal age in the AC group was higher compared with spontaneously conceiving women, as well as the proportion of

nulliparous women. Hypertensive disorders (both hypertension and preeclampsia) occurred more frequently in the AC group (20.2% vs. 16.2%, $p = 0.008$). This was mainly due to an increased incidence of preeclampsia in the AC group ($p < 0.001$). However, after correction for maternal age and parity this association was no longer significant (OR 1.0, 95% CI 0.8–1.2). Neonatal complications occurred more often in the spontaneously conceived twin group, with a significantly higher incidence of very preterm delivery and subsequently more admissions to a neonatal intensive care unit (NICU), more infants with a very low birthweight (<1500 g) and neonatal morbidity. Also, intrauterine fetal demise occurred significantly more often in spontaneously conceived twins (1.4% vs. 0.4%,

Table 3. Pregnancy characteristics and outcome of spontaneous and assisted conceived monochorionic twins.

	Monochorionic twins		p-value	OR (95% CI)
	Spontaneous conception (n = 223)	Assisted conception (n = 29)		
Maternal age, years (mean ± SD)	31.4 ± 4.8	33.7 ± 3.1	<0.001	
Age ≥35 years, n (%)	53 (23.7)	24 (41.4)	0.004	4.4 (2.3–8.5)
Parity, n (median, range)	0 (0–8)	0 (0–3)	0.002	
Nulliparous, n (%)	95 (42.7)	23 (79.3)	<0.001	7.5 (3.6–15.5)
Imminent preterm labor, n (%)	42 (18.8)	4 (13.8)	0.353	
Hypertensive disorders, n (%)	31 (13.9)	7 (24.1)	0.040	2.0 (1.0–3.8)
Pregnancy-induced and pre-existing hypertension, n (%)	17 (7.6)	3 (10.3)	0.467	
Preeclampsia, n (%)	17 (7.6)	4 (13.9)	0.108	
Diabetes, n (%)	5 (2.2)	3 (10.3)	0.001	5.0 (1.8–14.4)
Cesarean section, n (%)	104 (47.2)	15 (54.4)	0.305	
Elective CS, n (%)	48 (21.7)	7 (22.4)	0.901	
Emergency CS, n (%)	56 (25.3)	9 (31.6)		
	n = 446 fetuses	n = 58 fetuses		
Gestational age, weeks (median, range)	36 ⁺⁴ (20 ⁺² –40 ⁺⁴)	36 ⁺³ (23 ⁺⁰ –37 ⁺²)	0.971	
<32 weeks, n (%)	60 (13.4)	8 (13.8)	0.938	
32–37 weeks, n (%)	212 (47.4)	26 (44.8)	0.709	
≥37 weeks, n (%)	174 (39.1)	24 (41.4)	0.744	
Birthweight, grams (mean ± SD)	2268 ± 610	2133 ± 681	0.118	
SGA, n (%)	63 (14.1)	10 (17.2)	0.526	
Low birthweight, n (%)	275 (61.5)	40 (69.0)	0.271	
Very low birthweight, n (%)	53 (11.9)	11 (19.0)	0.126	
Mortality				
IUFD, n (%)	11 (2.5)	1 (1.7)	0.729	
Early NND, n (%)	13 (2.9)	2 (3.4)	0.820	
Late NND, n (%)	0	2 (3.4)	<0.001	N/C
Neonatal morbidity ^a				
RDS, n (%)	35 (7.8)	11 (19.0)	0.006	2.8 (5.3–2.8)
IVH, n (%)	13 (2.9)	2 (3.4)	0.820	
NEC, n (%)	8 (1.8)	5 (8.6)	0.002	5.2 (1.6–16.4)
Sepsis, n (%)	36 (8.1)	3 (5.2)	0.439	
Major neonatal morbidity, n (%) ^a	64 (14.3)	14 (24.1)	0.052	
Admission to NICU, n (%) ^a	102 (22.8)	16 (27.6)	0.420	

Abbreviations: CI, confidence interval; CS, cesarean section; IUFD, intrauterine fetal death; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; OR, odds ratio; RDS, respiratory distress syndrome; SGA, small for gestational age.

^aExcluding intrauterine fetal deaths.

$p = 0.011$); there were no differences in neonatal death rates.

Tables 2 and 3 show outcome of patients who conceived spontaneously or by AC according to chorionicity. In both MC and DC twin pregnancies, mean maternal age and the proportion of nulliparous women were higher in the AC group, which was also associated with hypertensive disorders and diabetes. Perinatal outcome of spontaneously conceived DC twins, however, was worse compared with their spontaneously conceived counterparts (with more frequently occurring very preterm birth before 32 weeks of gestation and subsequently higher incidences of very low birthweight). This was in contrast to the worse perinatal outcome of MC twins after AC in

comparison to spontaneously conceived MC twins (with a higher incidence of neonatal morbidity such as RDS and NEC, and late neonatal deaths).

Tables 4 and 5 shows outcomes for AC twins by chorionicity. Perinatal outcome of MC twins after AC was significantly worse compared with DC twins conceived by assisted reproduction.

Discussion

Studies on perinatal outcome of twin pregnancies after AC show conflicting results. Due to the unequally distributed proportion of MC twins in spontaneously and AC-conceived twins most results from the literature

Table 4. Comparison of mono- and dichorionic twin by spontaneous conception.

	Spontaneous conception		<i>p</i> -value	OR (95% CI)
	Monochorionic twins (<i>n</i> = 223)	Dichorionic twins (<i>n</i> = 508)		
Maternal age, years (mean ± SD)	31.4 ± 4.8	32.5 ± 4.5	<0.001	
Age ≥35 years, <i>n</i> (%)	53 (23.7)	176 (34.6)	<0.001	1.6(1.2–2.1)
Parity (median, range)	0 (0–8)	1 (0–5)	0.548	
Nulliparous, <i>n</i> (%)	95 (42.7)	214 (42.1)	0.830	
Imminent preterm labor, <i>n</i> (%)	42 (18.8)	108 (21.3)	0.281	
Hypertensive disorders, <i>n</i> (%)	31 (13.9)	87 (17.2)	0.109	
Pregnancy-induced and pre-existing hypertension, <i>n</i> (%)	17 (7.6)	27 (5.4)	0.106	
Preeclampsia, <i>n</i> (%)	17 (7.6)	56 (11.0)	0.045	1.7 (1.1–2.5)
Diabetes, <i>n</i> (%)	5 (2.2)	22 (4.3)	0.050	1.8 (0.9–3.7)
Cesarean section, <i>n</i> (%)	104 (47.2)	247 (48.9)	0.554	
Elective CS	48 (21.7)	89 (17.5)	0.059	
Emergency CS	56 (25.3)	158 (31.3)	0.223	
	<i>n</i> = 446 fetuses	<i>n</i> = 1016 fetuses		
Gestational age, weeks (median, range)	36 ⁺⁴ (20 ⁺² –40 ⁺⁴)	37 ⁺¹ (23 ⁺² –41 ⁺³)	<0.001	
<32 weeks, <i>n</i> (%)	60 (13.4)	122 (12.0)	0.450	
32–37 weeks, <i>n</i> (%)	212 (47.4)	344 (33.9)	<0.001	0.5 (0.3–0.7)
≥37 weeks, <i>n</i> (%)	174 (39.1)	550 (54.1)	<0.001	1.8 (1.5–2.3)
Birthweight, grams (mean ± SD)	2268 ± 610	2471 ± 679	<0.001	
SGA, <i>n</i> (%)	63 (14.1)	166 (16.5)	0.258	
Low birthweight, <i>n</i> (%)	275 (61.5)	462 (45.5)	<0.001	0.7 (0.5–0.9)
Very low birthweight, <i>n</i> (%)	53 (11.9)	105 (10.3)	0.388	
Mortality				
IUFD, <i>n</i> (%)	11 (2.5)	10 (1.0)	0.029	0.3 (0.1–0.8)
Early NND, <i>n</i> (%)	13 (2.9)	16 (1.6)	0.246	
Late NND, <i>n</i> (%)	0	3 (0.3)	0.250	
Neonatal morbidity ^a				
RDS, <i>n</i> (%)	35 (7.8)	69 (6.8)	0.476	
IVH, <i>n</i> (%)	13 (2.9)	23 (2.3)	0.464	
NEC, <i>n</i> (%)	8 (1.8)	6 (0.6)	0.030	0.4 (0.1–1.2)
Sepsis, <i>n</i> (%)	36 (8.1)	46 (4.5)	0.007	0.6 (0.3–1.1)
Major neonatal morbidity, <i>n</i> (%) ^a	64 (14.3)	107 (10.5)	0.038	0.7 (0.5–1.0)
Admission to NICU, <i>n</i> (%) ^a	102 (22.8)	151 (14.9)	<0.001	0.6 (0.4–0.8)

Abbreviations: CI, confidence interval; CS, cesarean section; IUFD, intrauterine fetal death; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; OR, odds ratio; RDS, respiratory distress syndrome; SGA, small for gestational age.

^aExcluding intrauterine fetal deaths.

Table 5. Comparison of monochorionic and dichorionic twin conceived by assisted reproduction.

	Assisted conception		p-value	OR (95% CI)
	Monochorionic twins (n = 29)	Dichorionic twins (n = 545)		
Maternal age, years (mean ± SD)	33.7 ± 3.1	33.9 ± 4.3	0.673	
Age ≥35 years, n (%)	24 (41.4)	256 (47.0)	0.405	
Parity (median, range)	0 (0–3)	0 (0–6)	0.038	
Nulliparous, n (%)	23 (79.3)	355 (65.1)	0.027	0.5 (0.2–1.0)
Imminent preterm labor, n (%)	4 (13.8)	126 (23.1)	0.098	
Hypertensive disorders, n (%)	7 (24.1)	109 (20.0)	0.444	
Pregnancy-induced and pre-existing hypertension, n (%)	3 (10.3)	33 (6.1)	0.189	
Preeclampsia, n (%)	4 (13.9)	79 (14.5)	0.882	
Diabetes, n (%)	3 (10.3)	18 (3.3)	0.005	0.2 (0.1–0.5)
Cesarean section, n (%)	15 (54.4)	261 (48.3)	0.370	
Elective CS	7 (22.4)	102 (18.8)	0.495	
Emergency CS	9 (31.6)	159 (29.4)		
	n = 58 fetuses	n = 1090 fetuses		
Gestational age, weeks (median, range)	36 ⁺³ (23 ⁺⁰ –37 ⁺²)	37 ⁺² (22 ⁺⁴ –41 ⁺⁶)	<0.001	
<32 weeks, n (%)	8 (13.8)	73 (6.7)	0.040	0.4 (0.1–1.6)
32–37 weeks, n (%)	26 (44.8)	394 (36.1)	0.181	
≥37 weeks, n (%)	24 (41.4)	622 (57.2)	0.018	1.9 (1.1–3.2)
Birthweight, grams (mean ± SD)	2133 ± 681	2475 ± 625	<0.001	
SGA, n (%)	10 (17.2)	169 (1.65)	0.736	
Low birthweight, n (%)	40 (69.0)	510 (46.8)	0.001	0.5 (0.2–1.0)
Very low birthweight, n (%)	11 (19.0)	81 (7.4)	0.002	0.3 (0.2–0.7)
Mortality				
IUFD, n (%)	1 (1.7)	14 (0.7)	0.126	
Early NND, n (%)	2 (3.4)	13 (1.2)	0.403	
Late NND, n (%)	2 (3.4)	1 (0.1)	<0.001	0.1 (0.0–0.3)
Neonatal morbidity ^a				
RDS, n (%)	11 (19.0)	59 (5.4)	<0.001	0.2 (0.1–0.5)
IVH, n (%)	2 (3.4)	21 (1.9)	0.420	
NEC, n (%)	5 (8.6)	8 (0.7)	<0.001	0.2 (0.4–1.1)
Sepsis, n (%)	3 (5.2)	40 (3.7)	0.557	
Major neonatal morbidity, n (%) ^a	14 (24.1)	94 (8.6)	<0.001	0.3 (0.2–0.6)
Admission to NICU, n (%) ^a	16 (27.6)	141 (12.9)	0.002	0.8 (0.3–2.1)

Abbreviations: CI, confidence interval; CS, cesarean section; IUFD, intrauterine fetal death; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NND, neonatal death; OR, odds ratio; RDS, respiratory distress syndrome; SGA, small for gestational age.

^aExcluding intrauterine fetal deaths.

cannot be interpreted clearly. Our study is one of the few studies in which chorionicity has been taken into account. Maternal age and incidence of nulliparity were higher among the study group. Obstetric complications occurred equally in both conception groups, irrespective of chorionicity, and potential differences could generally be explained by the differences in maternal age and parity between both groups. There were, however, differences in neonatal outcome; spontaneously conceived twins were born earlier than twins after AC, with subsequent lower birthweights and more admissions to NICU with increased neonatal morbidity. Monochorionic twins have worse pregnancy outcomes compared with DC twins, irrespective of mode of conception; MC twins conceived

by assisted reproduction have worse perinatal outcome compared with spontaneously conceived MC twins.

Limitations of our study included the retrospective character and the fact that it was not entirely population based. The data should therefore be interpreted with care because a selection bias may have been introduced due to the specific nature of tertiary referral centers. However, we included only pregnancies with antenatal care from the first trimester onwards so that referred twin pregnancies with a possible unfavorable outcome could not bias the results.

In general, when comparing twins after spontaneous and assisted conception, hypertensive disorders occur more frequently in AC twin pregnancies. This appeared

to be due to a larger proportion of elderly nulliparous patients in this group. Similar results have been reported before (7,8). Another factor known to influence the incidence of hypertensive disorders in the AC group is sperm donation by an “anonymous” donor (i.e. new paternity).

It is commonly known that MC twins carry higher risks of adverse obstetric and perinatal outcome, for example, lower gestational age, lower birthweight and a higher incidence of both NICU admission and neonatal morbidity (9). Given the higher incidence of MC twins in the spontaneously conceived group we expected overall perinatal outcome to be poorer in that group (10), which was indeed the case. However, our data are in contrast to four partly overlapping systematic reviews in which higher risks for cesarean delivery, preterm birth and low birthweight were found in AC twins (11–14). It is difficult to explain the different findings in our study group. However, it may well be that management in AC twins is more aggressive than in spontaneously conceived twins, with higher rates of obstetric interventions. Our data seem to indicate that such a policy – if indeed present – is not justified.

When analyzed by mode of conception and chorionicity, we found only a few differences in outcome between spontaneously and AC-conceived twins. In AC-conceived DC twins outcome was slightly better than in spontaneously conceived DC twins, whereas in MC twins the opposite was found. These data are remarkably similar to those of the only other study in which perinatal outcome was studied in spontaneous and AC-conceived twin pregnancies with either DC or MC placentation (15). Those authors found more antepartum admissions, admissions to the NICU and more NEC in spontaneous DC twins than in AC-conceived DC twins. In AC-conceived MC twins they found a higher incidence of placenta previa, but in spontaneous MC twins the incidence of low birthweight was higher.

In several studies, chorionicity was also taken into account. In two studies there was matching for zygosity (16,17), in another four studies only unlike-sex pairs were included (18–21) in order to select (some of) dizygotic twins and in three other studies (22–24) a sub-analysis was made on naturally conceived dizygotic twins compared with AC twins to rule out the negative effect of monochorionicity on outcome. Finally, recent publications that have only included DC twin pregnancies (25–30) and a recent meta-analysis on outcome of DC twins after assisted reproduction show that these twins are at increased risk of poor outcome, such as preeclampsia, preterm birth and cesarean section, but no significant adverse effect on neonatal outcome (31). In the present study we did find an increased risk of preeclampsia in DC twins after AC, but risk of preterm birth with low

birthweight was increased in the spontaneously conceived DC group (without neonatal adverse effect).

Publications regarding outcome of MC twins conceived by infertility treatments are scarce. There are currently only four studies available; two of these studies report on worse perinatal outcome in MC twins by AC (32,33) and the other two studies found similar outcomes in AC and spontaneous MC twins (34,35). In a historical cohort study from France ($n = 1580$) comparable to our study there was no increased risk of obstetric and neonatal complications after adjustment for maternal factors and chorionicity (36). In our study, neonatal morbidity (mainly RDS and NEC) and late neonatal death occurred more often in MC twins after AC, which is in line with two previous studies (32,33). The underlying mechanism involved in the association between AC and perinatal risks in these pregnancies is unclear.

In conclusion, spontaneously conceived twins have worse pregnancy outcome compared with twins after AC. Overall, perinatal outcome was better in the AC twins probably due to a lower incidence of monochorionicity. The latter data are largely in contrast with systematic literature reviews, which describe a higher incidence of cesarean deliveries, preterm birth and low birthweight infants in AC twin pregnancies. We suggest that poorer outcome in those studies might be related to higher (iatrogenic) obstetric intervention rates. The already increased perinatal risks in MC twins are even higher in MC twins conceived after infertility treatments compared with spontaneously conceived MC twins, which warrants extra attention to these high-risk pregnancies.

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