Thieme

Is There a Cumulative Effect for Congenital Heart Defects in Monochorionic Twins after Assisted Reproduction? – A Retrospective Analysis at a Tertiary Referral Center

Gibt es einen kumulativen Effekt für angeborene Herzfehler in monochorialen Zwillingen nach assistierter Reproduktion? – Eine retrospektive Analyse in einem Klinikum der Maximalversorgung

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ABSTRACT

Introduction
The aim of our study was to compare maternal, chorionicity and neonatal complications in monochorionic (MC) twins between spontaneously conceived (SC) and assisted reproductive technologies (ART) pregnancies.

Material and Methods
This was a retrospective cohort study between January 2010 to December 2019 at a tertiary referral University center. All consecutive pregnancies with MC twins that delivered at our University hospital were included. Maternal, chorionicity and neonatal complications were recorded and compared between SC and ART pregnancies.

Results
393 MC pregnancies were included for final analysis, including 353 (89.8%) SC and 40 (10.2%) pregnancies conceived after ART. Hypothyroidism was the only maternal condition seen significantly more often in ART pregnancies (35.0% vs 12.5%, p = 0.001). There were no significant differences in chorionicity complications, such as twin-twin transfusion syndrome, selective fetal growth restriction and twin anemia-polycythemia sequence (40.0% in ART pregnancies vs 31.6% in SC pregnancies, p = 0.291). At least one congenital anomaly in one twin was seen significantly more often in ART pregnancies (18.8% vs 8.1%, p = 0.004), especially congenital heart defects (16.3% vs 6.2%, p = 0.005). There were

no other significant differences in neonatal outcomes between both groups, however, there were non-significant trends in gestational age at delivery (34 weeks in ART pregnancies vs 35 weeks, p = 0.078) and birthweight (1951 g ± 747 in ART pregnancies vs 2143 g ± 579, p = 0.066).

Conclusion

This is the largest cohort study to date comparing maternal, chorionicity and neonatal complications between MC twin pregnancies after ART and after SC. Hypothyroidism was the only maternal condition occurring more frequently in pregnancies conceived after ART. There were no significant differences in chorionicity complications, in contrast to previously reported studies. While MC twins and ART pregnancies per se are known to be at risk for congenital heart defects, there seems to be a cumulative effect in MC pregnancies conceived after ART.

ZUSAMMENFASSUNG

Einleitung

Das Ziel dieser Studie war es, die mütterlichen, neonatalen und chorionizitätsbedingte Komplikationen von monochorialen (MC) Zwillingen bei spontan gezeugten (SG) bzw. mit Techniken der assistierten Reproduktion (ART) gezeugten Kindern zu vergleichen.

Material und Methoden

Diese retrospektive Kohortenstudie untersucht den Zeitraum von Januar 2010 bis Dezember 2019 in einem Universitätsklinikum der Maximalversorgung. Alle konsekutiven in unserem Universitätskrankenhaus entbundenen Schwangerschaften mit MC Zwillingen wurden in die Studie aufgenommen. Die mütterlichen, neonatalen und chorionizitätsbedingten Komplikationen wurden aufgezeichnet und ihr Auftreten in SG- und ART-Schwangerschaften wurde verglichen.

Ergebnisse

Insgesamt wurden 393 MC Schwangerschaften in die Endanalyse aufgenommen, davon waren 353 (89,8 %) SG- und 40 (10,2 %) ART-Schwangerschaften. Die Schilddrüsenunterfunktion war die einzige mütterliche Komplikation, die signifikant häufiger bei ART-Schwangerschaften auftrat (35,0 % vs. 12,5 %, p = 0,001). Es gab keine signifikanten Unterschiede in den chorionizitätsbedingten Komplikationen wie fetofetales Transfusionssyndrom, selektive fetale Wachstumsrestriktion und Zwillings-Anämie-Polyzythämie-Sequenz (40,0 % in ART-Schwangerschaften vs. 31,6 % in SG-Schwangerschaften, p = 0,291). Bei ART-Schwangerschaften trat mindestens eine angeborene Anomalie bei einem Zwilling signifikant häufiger auf (18,8 % vs. 8,1 %, p = 0,004), insbesondere angeborene Herzfehler (16,3 % vs. 6,2 %, p = 0,005). Es gab keine anderen signifikanten Unterschiede in den neonatalen Outcomes zwischen beiden Gruppen; es gab aber nichtsignifikante Trends hinsichtlich des Schwangerschaftsalters bei der Entbindung (34 Wochen für ART-Schwangerschaften vs. 35 Wochen, p = 0,078) und des Geburtsgewichts (1951 g ± 747 für ART-Schwangerschaften vs. 2143 g ± 579, p = 0,066).

Schlussfolgerung

Es handelt sich hier um die bislang größte Kohortenstudie, die mütterliche, neonatale und chorionizitätsbedingte Komplikationen in MC Zwillingsschwangerschaften untersucht und das Auftreten von Komplikationen in ART-Schwangerschaften mit denen in SG-Schwangerschaften vergleicht. Die Schilddrüsenunterfunktion war die einzige mütterliche Komplikation, die häufiger bei ART-Schwangerschaften auftat. Im Gegensatz zu früheren Studien gab es keine signifikanten Unterschiede in den chorionizitätsbedingten Komplikationen. Während MC Zwillinge und ART-Schwangerschaften bekanntlich ein höheres Risiko für angeborene Herzfehler haben, scheint es einen kumulativen Effekt bei mit ART gezeugten MC Schwangerschaften zu geben.

Introduction

Pregnancies conceived after assisted reproductive technologies (ART) have been on the rise since its implementation more than 40 years ago, their incidence being currently at an estimated 6 % [1]. ART pregnancies are known to be associated with more maternal and neonatal complications than spontaneously conceived (SC) pregnancies, including ante- and postpartum hemorrhage, placental anomalies, gestational diabetes, hypertensive disorders on the maternal and preterm birth, low birthweight and neonatal morbidity and mortality on the neonatal side [2, 3, 4, 5, 6]. Multiple pregnancies are reported to be as high as 27% after ART [2, 3]. Monochorionic (MC) pregnancies comprise up to 2.5% of ART pregnancies. So far, studies regarding maternal and neonatal outcomes have focused mostly on singleton or dichorionic (DC) twin pregnancies following ART assuming that the risk profile in dichorionic twins is similar to singletons.

MC pregnancies are associated with chorionicity complications for the fetus [7]. They may develop twin to twin transfusion syndrome (TTTS) in about 15%, selective fetal growth restriction (sFGR) in 10–15%, twin anemia-polycythemia sequence (TAPS) in about 6% and twin reversed arterial perfusion (TRAP) in approximately 1% [8, 9, 10, 11, 12, 13, 14, 15]. In addition, MC pregnancies have a higher risk for congenital anomalies, especially congenital heart defects [16]. Regarding maternal and peripartum complications, hypertensive disorders, gestational diabetes and postpartum hemorrhage are seen more frequently in MC pregnan-

cies than in singletons [16]. Furthermore, MC twins are subjected to iatrogenic preterm birth as delivery in uncomplicated pregnancies is usually recommend around 36 weeks of gestation for MC pregnancies and around 33 weeks of gestation for monoamniotic pregnancies [6, 17, 18]. Current guidelines recommend close monitoring of monochorionic twin pregnancies [6, 12, 16, 19].

Previous studies examining complications in MC pregnancies after ART mainly looked at maternal complications in different conception methods and did not include typical MC complications, such as TTTS or TAPS [20, 21]. In addition, most studies focused on dichorionic (DC) pregnancies only or did not discriminate between MC and DC pregnancies [22, 23, 24]. To date, for MC pregnancies after ART, fetal and maternal risks have not yet been sufficiently studied [25].

The aim of our study was to compare maternal, chorionicity and neonatal complications in ART and SC pregnancies in MC twins.

Material and Methods

This was a retrospective cohort study of monochorionic twin pregnancies delivered between January 2010 and December 2019 at a single tertiary referral center. All MC pregnancies above the limit of viability (≥ 24 weeks of gestation) that delivered at our center were included. Prenatal surveillance of twin pregnancies was performed according to standard guidelines, irrespective of mode of conception [6]. Fetal and obstetrical data were stored prospectively in an electronic database. If mode of conception was not recorded in the database, physical patients' charts were reviewed for further information. For neonatal outcome, data were collected from the neonatal electronic database. Postpartum hemorrhage (PPH) was defined according to guidelines as a blood loss of ≥ 500 ml after vaginal delivery and ≥ 1000 ml after Cesarean delivery [26]. Hypertensive disorders in pregnancy were classified according to international guidelines [27, 28].

Inclusion criteria for our final analysis were SC MC pregnancies and MC pregnancies conceived after ART, including intracytoplasmic sperm injection (ICSI), in vitro fertilization (IVF) or egg donation. Exclusion criteria were unknown mode of conception and intrauterine demise of both fetuses.

We compared the incidences of chorionicity complications specific to MC twins as well as maternal complications, including preeclampsia/HELLP syndrome, preterm contractions, postpartum hemorrhage (defined as blood loss ≥ 500 ml at vaginal delivery and ≥ 1000 ml at Cesarean delivery), preterm premature rupture of membranes (PPROM), preterm birth, and peripartum as well neonatal outcome between SC and ART pregnancies. Postnatal hospitalization occurred according to local standard. We recorded immediate hospitalization after delivery of at least one twin and congenital anomalies. Multiple findings were possible.

Statistical analysis

Statistical analyses were performed using the statistical software SPSS for Windows, Version 24.0 (SPSS Inc. U.S.A.). Continuous (metric) variables were summarized using descriptive statistics, including arithmetic mean, standard deviation, median, lower (25^{th} percentiles) and upper (75^{th} percentiles) quartile, minimum and maximum. Categorical variables were summarized by the number of cases and percentages (%).

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Most of the variables tested did not show a normal distribution (Kolmogorov-Smirnov test: $p < 0.05$). Non-parametric tests for non-normally distributed samples were used. Mann-Whitney U test for the intergroup comparison of groups with respect to continuous data. Chi-square (Chi^2) test or Fisher's exact test for the intergroup comparison with respect to categorical variables. All statistical tests were performed with a two-tailed alpha of 0.05. All confidence intervals were calculated using 95 % confidence intervals. Test results with $p < 0.05$ were regarded as statistically significant.

Ethics statement

This study was conducted in accordance with the ethical guidelines of the WMA General Assembly Declaration of Helsinki. Ethical approval was granted by Medical Ethics Committee of the Medical Association of Hamburg (Ethik-Kommission der Ärztekammer Hamburg). All patients declared written consent.

Results

Study population and chorionicity complications

A total of 408 MC pregnancies were identified. 154 cases have already been studied for the development of TAPS purposes [10]. In 14 of 408 cases (3.4%), mode of conception could not be determined. One case was excluded with intrauterine fetal demise (IUFD) of both twins at 30 weeks of gestation in a patient with a SC pregnancy, leaving 393 MC pregnancies for final analysis. 353 (89.8%) pregnancies were SC, and 40 (10.2%) pregnancies were conceived after ART (13 IVF, 25 ICSI and two cases with egg donation).

Maternal demographics and complications are summarized in ▶ **Table 1** and ▶ **Fig. 1a**. Women with ART pregnancies were significantly older (37.1 ± 5.5 years vs 32.3 ± 5.1 years, $p < 0.001$) and had significantly fewer pregnancies at inclusion (median [range] = 0 [0–2] vs 0 [0–5], $p < 0.001$). Hypothyroidism occurred significantly more often in ART pregnancies in comparison to SC pregnancies (35.0% vs 12.5%, $p = 0.001$). Diagnosis of hypothyroidism was adopted from patient charts if treatment occurred. There were no significant differences in ART vs SC pregnancies in chorionicity complications, with TTTS (22.5% vs 15.6%, $p = 0.26$), sFGR (10.0% vs 9.1%, $p = 0.77$) and TAPS (0.0% vs 3.4%, $p = 0.62$). Chorionicity complications are summarized in ▶ **Table 2** and ▶ **Fig. 1b**.

Peripartum outcomes

Peripartum outcomes are summarized in ▶ **Table 3**. Mean gestational age at delivery was lower in ART pregnancies at 34 weeks vs 35 weeks ($p = 0.078$), with more cases delivered below 32 weeks in that group (30.0% vs 18.4%, $p = 0.093$). There were more cases in ART pregnancies with a Cesarean delivery (82.5% vs 68.8%), but there was no significant difference in delivery mode between both groups ($p = 0.115$). Indication for Cesarean delivery included breech or transverse presentation of the leading twin, abnormal

▶**Table 1** Maternal demographics and pregnancy complications. Data are given either in n (%), median [range] or mean (± standard deviation). A p value ≤ 0.05 was considered statistically significant.

	SC (n = 353)	ART (n = 40)	p value
Maternal age, years (mean ± standard deviation)	32.3 ± 5.1	37.1 ± 5.5	< 0.001
BMI before pregnancy, kg/m^2 (mean ± standard deviation)	24.1 ± 5.0	23.29 ± 4.1	0.367
BMI ≥ 25 kg/m^2	112 (31.7 %)	16 (40.0 %)	0.089
Parity (median, range)	0 [0–5]	0 [0–2]	< 0.001
Smoking	14 (4.0 %)	0 (0.0 %)	0.378
Hypothyroidism	44 (12.5 %)	14 (35.0 %)	0.001
Thromboembolic events in or before pregnancy	6 (1.7 %)	1 (2.5 %)	0.531
Pre-existing thromboembolic conditions	7 (2.0 %)	2 (5.0 %)	0.230
Autoimmune diseases	13 (3.7 %)	0 (0.0 %)	0.378
Pulmonary diseases	6 (1.7 %)	0 (0.0 %)	1.000
Gestational diabetes or type II diabetes	26 (7.4 %)	6 (15.0 %)	0.119
Hypertensive disorders of pregnancy (overall patients)	27 (7.6 %)	6 (15.0 %)	0.113
▪ Pregnancy-induced hypertension	3 (0.85 %)	1 (5.0 %)	0.325
▪ Pre-existing arterial hypertension	4 (1.1 %)	2 (2.5 %)	0.059
▪ Preeclampsia/HELLP	20 (5.7 %)	3 (7.5 %)	0.640
Onset of preeclampsia/HELLP, GA (mean, range)	35 [27–37]	35 [32–36]	0.906
Cholestasis of pregnancy	13 (3.7 %)	0 (0.0 %)	0.378

ART = assisted reproductive technologies; BMI = body mass index; GA = gestational age; HELLP = hemolysis, elevated liver enzymes, low platelets; SC = spontaneous conception

▶**Table 2** Chorionicity complications. A p value ≤ 0.05 was considered statistically significant.

	SC (n = 353) n (%) median [range]	ART (n = 40) n (%) median [range]	p value
MCMA twins	20 (5.7 %)	1 (2.5 %)	0.710
At least one complication of monochorionicity	112 (31.6 %)	16 (40.0 %)	0.38
▪ TTTS	55 (15.6 %)	9 (22.5 %)	0.26
▪ TAPS	12 (3.4 %)	0 (0.0 %)	0.62
▪ sFGR	32 (9.1 %)	4 (10.0 %)	0.77
▪ TTTS and sFGR	9 (2.5 %)	2 (5.0 %)	0.31
▪ TAPS and sFGR	4 (1.1 %)	1 (2.5 %)	0.42
Laser treatment for TTTS	52 (14.7 %)	9 (22.5 %)	0.247
GA at laser treatment for TTTS, weeks	21 [17–28]	23 [19–28]	0.307

ART = assisted reproductive technologies; GA = gestational age; MCMA = monochorionic monoamniotic; SC = spontaneous conception; sFGR = selective fetal growth restriction; TAPS = twin anemia polycythemia sequence; TTTS = twin to twin transfusion syndrome

Doppler findings in at least one twin, monochorionic monoamniotic (MCMA) twins or elective Cesarean delivery owing to maternal decision. There was no significant difference between both groups regarding induction of labor (17.5% in ART pregnancies and 21.0% in SC pregnancies, p = 0.685). Indication for induction included PPROM, abnormal Doppler findings in at least one twin as well as gestational age in MC twin pregnancies according to guidelines. PPH occurred in 10.0% in ART pregnancies and in 9.6% in SC pregnancies (p = 1.00).

Neonatal outcomes

Neonatal outcomes are summarized in ▶ **Table 4**. There was only one (2.5%) IUFD in ART pregnancies compared to 16 (4.5%) in SC pregnancies (p = 0.789).

Structural anomalies occurred significantly more often in ART than in SC pregnancies (18.8% vs 8.1%, p = 0.004, ▶ **Table 5**). This could be traced back to a significantly higher incidence of congenital heart defects in ART than in SC pregnancies (16.3% vs 6.2%, p = 0.005). Most of these were isolated ventricular and atrial septal defects in both groups. Further postnatal echocardiographic findings in SC pregnancies were septal defects with pulmonary stenosis, tricuspid regurgitation, Ebstein's anomaly, second degree atrioventricular block, tetralogy of Fallot, double outlet right ventricle, hypoplastic left heart syndrome as well as dextrocardia. In ART pregnancies, cases of right ventricular hypoplasia with hypertrophy and pulmonary stenosis, truncus arteriosus communis with mitral valve anomaly as well as tetralogy of Fallot were also found.

Discussion

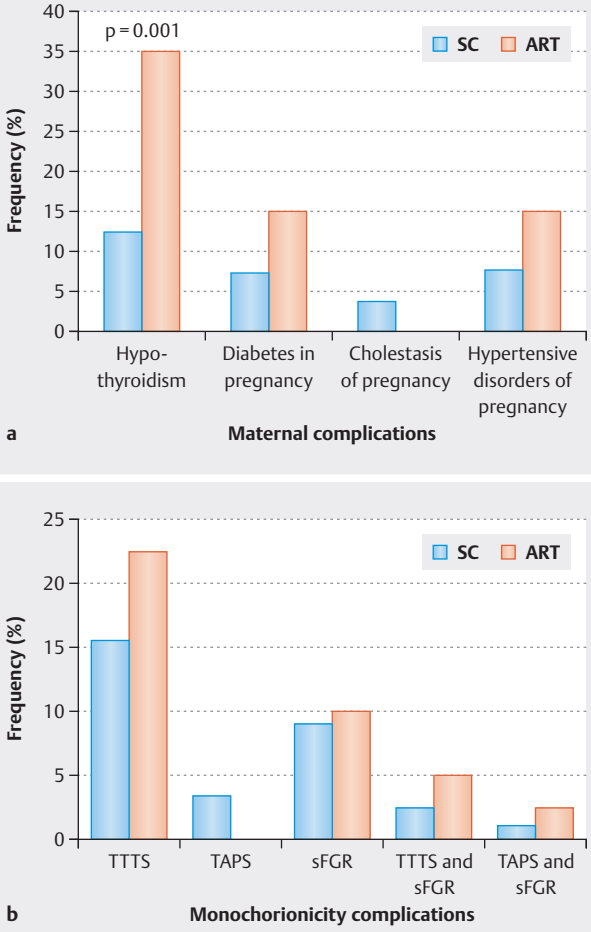
To our knowledge, this is the largest study focusing on maternal, chorionicity and neonatal complications comparing MC pregnancies after spontaneous conception vs ART pregnancies.

Hypothyroidism was the only maternal complication occurring more frequently in MC pregnancies after ART, and has been associated with infertility [29]. In contrast to a meta-analysis that found MC ART pregnancies at a higher risk for gestational diabetes and hypertension in pregnancy [30], we did not see any other significant differences in maternal complications in this group.

There were no significant differences in chorionicity complications between the two groups in our study. Other studies have mainly focused on TTTS only when comparing both groups, and did not see any differences in TTTS between ART and SC pregnancies as reported in a meta-analysis [31], in contrast to a study that observed a higher incidence of TTTS in SC pregnancies [32].

Congenital fetal anomalies occurred significantly more often in pregnancies conceived after ART, as expected and previously described for overall ART pregnancies, but data on multiple pregnancies as well as specific details on what kind of anomalies are missing [33, 34]. Cerebral and urogenital anomalies occurred more frequently after ART as expected, however, the difference was not significant compared to SC pregnancies.

In our population, congenital heart defects occurred significantly more often in MC pregnancies conceived after ART, at a surprisingly higher number than previously reported with 2–8% [35]. MC twins are known to have a higher risk for congenital heart defects and this risk seems to increase in pregnancies conceived after ART [35, 36, 37]. The most common congenital heart defects were atrial and ventricular septal defects in both groups in our study. As we are a tertiary referral center for congenital heart defects with an interdisciplinary approach, fetuses from a broad geographical area are referred to us, independent of mode of conception upon referral.



▶ **Fig. 1** **a** Comparison of maternal complications in spontaneously conceived (SC) pregnancies and in assisted reproductive technologies (ART) pregnancies. **b** Comparison of monochorionicity complications in spontaneously conceived (SC) pregnancies and in assisted reproductive technologies (ART) pregnancies.

Apart from congenital heart defects, we did not find an increase in any other neonatal complications after ART, which is in accordance with other studies [38, 39]. Previous studies have shown a higher risk for lower birthweight in twin ART pregnancies [40]. In our study, ART pregnancies were delivered at an earlier gestational age (34 weeks) which could explain the lower birthweight in this group. Nevertheless, this might be due to ART pregnancies being delivered one week earlier. Women with ART pregnancies delivered more often via Cesarean section in our study, as was also seen in previous studies [41, 42].

Strengths include the focus on MC pregnancies with different modes of conception. As this study was performed at a single cen-

▶**Table 3** Peripartum outcomes. A p value ≤ 0.05 was considered statistically significant.

	SC (n = 353) n (%) median [range]	**ART (n = 40)** n (%) median [range]	**p value**
Gestational age at delivery, weeks (mean)	35	34	0.078
Premature delivery < 32 weeks	65 (18.4 %)	12 (30.0 %)	0.093
PPROM < 32 weeks of gestation	27 (7.6 %)	6 (15.0 %)	0.339
Delivery mode			
▪ Both SVD	106 (30.0 %)	6 (15.0 %)	0.06
▪ Both CS	243 (68.8 %)	33 (82.5 %)	0.10
▪ First SVD, second CS	4 (1.1 %)	1 (2.5 %)	0.42
Induction of labor	74 (21.0 %)	7 (17.5 %)	0.685
Blood loss, ml (mean ± standard deviation, range)	484 ± 332 [200–3000]	554 ± 349 [200–3000]	0.005
PPH	34 (9.6 %)	4 (10.0 %)	1.000
▪ Uterine atony	14 (39.7 %)	2 (50.0 %)	
▪ Placental retention	11 (31.2 %)	1 (25.0 %)	
▪ PAS	3 (8.5 %)	0 (0.0 %)	
▪ Placenta previa	1 (2.8 %)	0 (0.0 %)	
▪ Placental abruption	2 (5.7 %)	0 (0.0 %)	
▪ Trauma	1 (2.8 %)	0 (0.0 %)	
▪ Not specified	2 (2.8 %)	1 (25.0 %)	

ART = assisted reproductive technologies; CS = Cesarean section; GA = gestational age; PAS = placenta accreta spectrum; PPH = postpartum hemorrhage; PPROM = premature rupture of membranes; SC = spontaneous conception; SVD = spontaneous vaginal delivery

▶**Table 4** Neonatal outcome. Data are given either in n (%), median [range] or mean (± standard deviation). A p value ≤ 0.05 was considered statistically significant.

	SC (n = 353)	**ART (n = 40)**	**p value**
Female	174 (49.3 %)	23 (57.5 %)	0.405
Male	178 (50.4 %)	17 (42.5 %)	
Birthweight, g (mean ± standard deviation)	2143 ± 579	1951 ± 74	0.066
Birthweight discordance, % (mean ± standard deviation)	13 ± 11	16.5 ± 14	0.186
Head circumference T1 (mean ± standard deviation)	32 ± 2.6	31 ± 3.0	0.284
Head circumference T2 (mean ± standard deviation)	31 ± 3.2	30.4 ± 3.2	0.172
Apgar at 5′ T1 (median, range)	9 [0, 10]	9 [6, 10]	0.323
Apgar at 5′ T2 (median, range)	9 [0, 10]	9 [5, 10]	0.774
Umbilical artery pH T1 (mean ± standard deviation)	7.31 ± 0.08	7.32 ± 0.08	0.683
Umbilical artery pH T2 (mean ± standard deviation)	7.30 ± 0.09	7.29 ± 0.07	0.167
Admission to NICU and IMC (pregnancies), n = 279	249 (63.4 %)	30 (75 %)	0.203
Perinatal death (within 7 days after delivery) of at least one twin	3 (0.9 %)	0 (0.0 %)	1.000
IUFD one twin	16 (4.5 %)	1 (2.5 %)	0.789
GA at IUFD (median, range)	26 [18–37]	29 [29]	0.706

ART = assisted reproductive technologies; GA = gestational age; IMC = intermediate care; IUFD = intrauterine fetal death; NICU = neonatal intensive care unit; SC = spontaneous conception; T1 = twin 1; T2 = twin 2

▶**Table 5** Fetal or neonatal anomalies. A p value ≤ 0.05 was considered statistically significant.

	SC (n = 706) n (%)	ART (n = 80) n (%)	p value
At least one anomaly in one twin	57 (8.1%)	15 (18.8%)	0.004
Congenital heart defects	44 (6.2%)	13 (16.3%)	0.005
Cerebral anomaly	6 (0.8%)	1 (1.3%)	0.530
Urogenital anomaly	3 (0.4%)	1 (1.3%)	0.350
Gastrointestinal anomaly	2 (0.3%)	0 (0.0%)	1.00
Other anomalies	6 (0.8%)	0 (0.0%)	1.00

ART = assisted reproductive technologies; SC = spontaneous conception

ter, homogeneity in care and treatment can be presumed. At the same time, we are a tertiary referral center with a heterogeneous patient cohort and interdisciplinary team. Patients are referred to us irrespective of mode of conception with suspected congenital heart defects. Important maternal characteristics such as information on hypertensive disorders of pregnancy were available. Furthermore, we also had access to perinatal as well as neonatal outcome, hence, were able to get accurate diagnosis of anomalies postnatally. One major limitation to our study is its retrospective character.

Conclusion

We did not see any significant differences regarding maternal or chorionicity complications between SC and ART MC pregnancies, in contrast to previously reported studies. However, owing to a higher incidence of congenital heart defects in ART pregnancies, the importance of a routine fetal echocardiography by an expert should be emphasized in MC pregnancies conceived after ART. More studies are needed to prospectively assess the data of congenital heart defects in this group.

Contributors' Statement

JZ: responsible for data acquisition, analysis and interpretation, writing of the manuscript. GY: responsible for data acquisition, analysis and interpretation, writing of the manuscript. AF: responsible for data acquisition and interpretation. KH: responsible for data analysis and interpretation, writing of the manuscript. MT: responsible for conception, data acquisition, analysis and interpretation, writing of the manuscript. All authors contributed to the design, drafting and the final version of the manuscript and approve the final submitted version.

Conflict of Interest

The authors declare that they have no conflict of interest.

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