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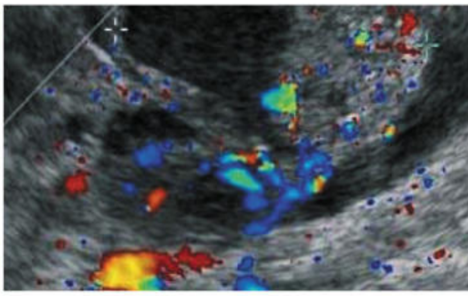

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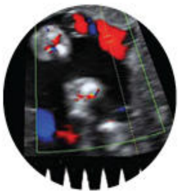

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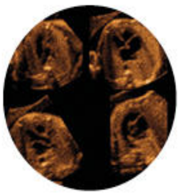

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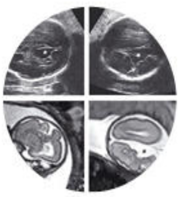

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Monochorionic twins after *in-vitro* fertilization: do they have poorer outcomes? A retrospective cohort study

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CONTRIBUTION

What are the novel findings of this work?

Monochorionic twins after IVF/ICSI have lower overall survival rates and have a higher risk of second trimester miscarriage

What are the clinical implications of this work?

Our paper may be useful in the counselling of patients with a monochorionic diamniotic twin gestation after IVF or ICSI

ABSTRACT:

OBJECTIVE: To compare the outcome of monochorionic diamniotic (MCDA) twin pregnancies after in vitro fertilisation with or without intracytoplasmic sperm injection (IVF/ICSI) with spontaneously conceived MCDA twins.

METHODS: Retrospective cohort study in MCDA twin pregnancies conceived after IVF/ICSI (N=80) or spontaneously (N=574), followed from the first trimester onward between January 2002 and September 2018 at a single centre. The primary outcome was survival per fetus from the first trimester until 28 days after birth. Secondary outcome measures were number of survivors, miscarriage, termination of pregnancy, intrauterine and neonatal demise, major congenital anomalies, twin-twin transfusion syndrome, selective intrauterine growth restriction, gestational age at birth, birth before 32 weeks, mode of delivery, neonatal intensive care admission, birthweight and birthweight discordance.

RESULTS: Overall survival was significantly lower in the IVF/ICSI group than in the spontaneous group (79% *versus* 90%, p = 0.001). Loss of one or both twins occurred twice as often in the IVF/ICSI group (29% *versus* 14%, p = 0.001) and there was a higher risk of second-trimester miscarriage (8% *versus* 1%, p = 0.002).

CONCLUSION: MCDA twins after IVF/ICSI have lower overall survival rates and higher rates of second-trimester miscarriage compared to spontaneously conceived MCDA twins.

INTRODUCTION

In vitro fertilization (IVF) increases the risk of monozygotic splitting from about 1 in 250 in spontaneous conceptions to 1 in 50 (1-3). In the case of a monozygotic split, ovulation induction and IVF also increase the risk of monochorionic placentation from 64% to 80% (4). IVF therefore increases the risk of monochorionic twinning. We also know that IVF is associated with increased risks of stillbirth, very preterm birth and other pregnancy-related complications in singletons (5-7). In twins, studies show conflicting results (8-11).

We do not know how IVF affects the outcome of monochorionic twin pregnancies, which are already at higher risk of adverse pregnancy outcomes than dichorionic pregnancies because of the vascular anastomoses and potential transfusion imbalances (12). IVF may further affect the outcome of these twins and given its increased use, it is necessary to understand the impact better. Studies on this topic are inconsistent (13-15). Some authors suggested lower survival rates in monochorionic diamniotic (MCDA) twins after IVF, but their results failed to show significance, likely due to small sample sizes (14, 16). Also, there are significant methodological differences between studies, making it hard to compare them. For example, many cohorts start from 20 weeks onward (17-19), while most losses in MCDA pregnancies occur before viability (20). Others do not differentiate between MCDA and monoamniotic twins (15).

Our study aims to compare the outcome between IVF and spontaneously conceived MCDA twins in an unselected cohort of MCDA twin pregnancies followed from the first trimester onward.

METHODS

Population and data collection

Patients diagnosed in the University Hospitals Leuven with an ongoing MCDA twin pregnancy in the first trimester (11+0 – 14+0 weeks) from January 2002 to September 2018 were included in the analysis. Monochorionic twin pregnancies are routinely referred to our hospital for alternating follow-up with a detailed ultrasound examination at 11-14, 16, 20, and 26 weeks of pregnancy. In addition to these four examinations, patients are instructed to have a sonographic assessment at least every two weeks, either at our center or the referring institution to timely detect twin-twin transfusion syndrome (TTTS) as per recommendation (12, 21). Patients referred explicitly for invasive testing or because of an anomaly were not included. Part of this cohort was included in earlier publications (12, 22-27).

In spontaneous conceptions, the crown-rump length of the larger twin determined gestational age (GA). In pregnancies resulting from IVF or intracytoplasmic sperm injection (ICSI), GA was defined using the date of egg retrieval in fresh cycles or embryonic age in frozen-thawed cycles. Pregnancies were classified according to the mode of conception: spontaneous versus in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI). Pregnancies resulting from ovulation induction were not included in the analysis in order to create a more homogenous study group and facilitate comparison to earlier published series (13, 14, 16, 28). Patients that conceived after insemination in a natural cycle, without ovulation induction, were included in the spontaneous conception group. Patients that conceived after egg donation were included in the IVF/ICSI group.

The primary outcome was fetal and neonatal survival between diagnosis in the first trimester (11+0 - 14+0 weeks) up to the first 28 days of life. The following secondary outcomes were studied: the number of survivors, miscarriage, termination of pregnancy, intrauterine and neonatal demise, major congenital anomalies, TTTS, selective intrauterine growth restriction (sIUGR), gestational age at birth, birth before 32 weeks, mode of delivery, neonatal intensive care admission, birth weight and birth weight discordance. Major congenital anomalies were defined according to the Eurocat-criteria as incompatible with life, requiring major surgery for correction or producing major dysfunction (29). The following maternal outcomes were reported: maternal death, eclampsia, uterine rupture, hysterectomy and intensive care unit (ICU) admission.

TTTS was defined as oligohydramnios in 1 twin (deepest vertical pool (DVP) < 2cm) and polyhydramnios in the other (DVP > 8cm before 20 weeks' gestation and DVP > 10cm from 20 weeks onward) (30). sIUGR was defined as a discordance in birthweight of 25% or more in the case of 2 live-born twins. If this information was not available, we used a discordance of 20% or more in estimated fetal weight on the last ultrasound before delivery or intrauterine demise. Laser coagulation of placental anastomoses is the first-line treatment for TTTS in our center. Also, in selected cases of sIUGR laser can be offered. Selective reduction by umbilical cord coagulation or by intrafetal radiofrequency ablation is offered in cases of discordant anomaly and selected cases of TTTS or sIUGR with predicted poor outcome for one of the twins. Patients can opt for termination of pregnancy in case of TTTS or preterm prelabour rupture of membranes prior to viability, as well as in cases of a major congenital anomaly in both twins.

Miscarriage was defined as spontaneous cervical dilation or spontaneous preterm prelabour rupture of membranes resulting in a delivery prior to 24 weeks in the absence of double intrauterine demise. Pregnancies with in utero demise of both twins before viability were not classified as miscarriages, but as pregnancies complicated by intrauterine demise.

Statistical analysis and sample size

Analysis on a fetal level was done using uni- and multivariate generalized estimated equation modelling to account for the clustering of twins within a twin pregnancy. For the analyses on pregnancy level, we compared continuous variables using the Student t-test or Mann-Whitney U test. Uni- and multivariate logistic regression analysis was performed to compare categorical variables and to adjust for potential confounders. The strength of association between the mode of conception (IVF/ICSI versus spontaneous) and the categorical outcomes was measured using odds ratio (OR). We then calculated adjusted odds ratios (aOR) to account for differences in maternal characteristics. As a secondary analysis, we looked at the differences between women that conceived with IVF and with ICSI. All analyses were performed using STATA 13.1 (StataCorp). 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). A 2-sided P-value of $P < .05$ was considered statistically significant.

We performed a sample size calculation to assess the required number of pregnancies to detect a clinically meaningful difference in the primary outcome. If we assume that 1 out of 10 MCDA twins originates after IVF/ICSI (12) and that IVF/ICSI would double the risk of loss of one or both twins from 15% after spontaneous conception (12) to 30%, then 610 pregnancies would be required (61 in the IVF/ICSI group and 549 in the control group) to achieve a power of at least 80% at a significance level (alpha) of 0.05 using a Pearson's Chi^2 test .

Ethical approval

Ethical approval for this retrospective cohort study was granted by the Ethics Committee of the University Hospitals Leuven (S62385).

RESULTS

Between January 2002 and September 2018, we followed 678 MCDA twin pregnancies from the first trimester onward. Three were lost to follow-up, and 21 underwent ovulation induction, which left 654 pregnancies available for analysis. Eighty women (12%) conceived with IVF/ICSI while 574 (88%) conceived spontaneously. IVF/ICSI patients were significantly older than those who conceived spontaneously (32 $\pm$ 4 years versus 30 $\pm$ 4 years; $p < 0.001$) and were more often nulliparous (54/80 (68%) versus 247/574 (43%); $p < 0.001$). In the IVF/ICSI group, all but two women were of Caucasian origin (3%), while there were 17 non-Caucasians in the spontaneous group (3%) (p=1.000). Of the 80 women in the IVF/ICSI group, 56 (70%) conceived after IVF, 20 (25%) after ICSI and 4 (5%) after egg donation.

The outcomes for IVF/ICSI and spontaneous pregnancies are summarized in Table I. Outcomes are reported on either fetal level (160 versus 1148 fetuses) or pregnancy level (80 versus 574 pregnancies). Fetal and neonatal survival was significantly lower in the IVF/ICSI group than in the spontaneous group (79% *versus* 90%, p = 0.001). Loss of one or both twins occurred twice as often in the IVF/ICSI group (29% *versus* 14%, p = 0.001). When we examined the different causes of fetal/neonatal loss, there was a higher risk of second-trimester miscarriage in the IVF/ICSI group. Median gestational age at miscarriage was 20+2 weeks (range 19+0 – 23+4) in the IVF/ICSI group and 21+3 weeks (range 15+1 – 23+1) in the spontaneous group (p = 0.519). All associations remained significant after adjustment for maternal age and parity. Although intra-uterine and neonatal death was more common in the IVF/ICSI-group, the difference did not reach statistical significance. Supplementary Table S1 provides details on the reasons for fetal and neonatal demise.

Supplementary Table S2 shows the comparison between the group that underwent IVF (56 cases) and the group that underwent ICSI (20 cases), excluding pregnancies after egg donation. We could not detect any significant differences between both groups.

There were no maternal deaths in our cohort, no eclampsia and no uterine rupture or hysterectomy. Two patients were admitted to ICU, both in the spontaneous conception group (1 for major postpartum hemorrhage and 1 for extreme hyperemesis with liver failure) (p = 1.000).

DISCUSSION

Our retrospective cohort study suggests a lower survival in monochorionic twins after IVF/ICSI (79%) compared to spontaneously conceived MCDA twin pregnancies (90%). We further observed a two-fold increased risk of losing one or both twins after IVF/ICSI (29% versus 14%). Also, the chance of taking home two babies is 15% lower after IVF/ICSI (71%) than after spontaneous conception (86%). These higher loss rates appear to be mainly related to an increased risk of second-trimester miscarriage.

We cannot explain the increased risk of second-trimester miscarriage in the IVF/ICSI group. In singletons, a recent large meta-analysis showed higher rates of stillbirth after IVF but no difference in the rate of second-trimester miscarriage (5). Twin pregnancies are known to be at increased risk of mid-trimester loss as compared to singletons (31, 32). However, most studies examining the impact of IVF on twin pregnancies either report on early miscarriages occurring before 12 weeks (33, 34). As our study included patients with ongoing MCDA twins in the first trimester, the miscarriages reported in our series are second-trimester miscarriages. Also, the few other studies that compare outcomes from the first trimester onwards do not distinguish between spontaneous miscarriage and intrauterine demise (16, 28), whereas most demises prior to 24 weeks are related to TTTS (17, 20, 35). Only the prospective cohort study by Sperling et al. studied miscarriage and fetal demise separately. They did not observe a difference in miscarriage rate MC twin pregnancies after assisted conception as compared to those conceived spontaneously (15). However, only 10 patients were included in the assisted conception group and monoamniotic twins and pregnancies conceived by ovulation induction were not excluded.

TTTS is the most important cause of excess mortality in monochorionic gestations (36), but its incidence was not elevated in the IVF/ICSI group. This in agreement with earlier publications (13, 14, 16, 28). One study even reported a lower incidence of TTTS after IVF (37), but the authors excluded pregnancies that resulted in the loss of one or both twins, while this is often the result of TTTS.

Mothers did well in our cohort, as shown by the low number of adverse maternal outcomes. However, the number of ICU admissions is likely to be underestimated. At our center, medium care is integrated in labor ward and therefore cases that are complicated by severe hemorrhage, pre-eclampsia or HELLP syndrome are only rarely admitted to ICU. Indeed, the two ICU admissions in our cohort were patients that were admitted in smaller centers. Records of estimated blood loss and/or transfusion would therefore provide more information, but since this is a retrospective study over a large period of time, this was not always properly recorded.

Since this is an observational study, our results do not prove that IVF/ICSI is the cause of the lower survival rates. Although the increase remained after correcting for maternal age and parity, other, unmeasured confounders may influence the risk besides fertility treatment. The subfertile woman that undergoes IVF/ICSI likely differs from the fertile woman that conceives naturally, and this may influence the pregnancy risk, rather than the fertility treatment itself, as was previously suggested in large cohorts of singletons and twins (5, 7, 16). Furthermore, late miscarriage after IVF is associated with the presence of leiomyomas and increased body mass index, two factors that could also play a role in decreased fertility (38). It would be interesting to examine the effect of smoking, body mass index, diabetes, hypertension, hormonal imbalances and so on. Unfortunately, as this is a retrospective study, we rely on ultrasound records that do not routinely include this information. We were only able to correct our results for maternal age and nulliparity. This is a shortcoming in our study.

There is also a possibility that the outcomes within the IVF/ICSI group differ according to the technique used. As such, fresh embryo transfer compared to frozen embryo transfer may be associated with higher risks of second-trimester miscarriage (39). We performed a subgroup analysis comparing pregnancies after IVF with those after ICSI, but were not able to demonstrate any differences between the groups. However, this does not prove that the groups truly do not differ, as the sample size in this analysis was low. Studies with a larger series of MCDA twin pregnancies after IVF/ICSI would be necessary to be able to distinguish between treatment methods.

The strength of our cohort is that we report on the largest series of unselected MCDA twin pregnancies from the first trimester onward. Most studies include patients from 20 to 24 weeks onwards (17-19), whereas most losses occur before viability, especially in monochorionic twins (12). Therefore, cohorts starting from the late second trimester will underestimate the true loss rate. Another strength is that we report exclusively on MCDA twins, while other authors often mixed monochorionic and dichorionic twins (10) or included monoamniotic pairs as well (15).

The rate of IVF/ICSI in our cohort was 12%, which may seem high compared to some series (14, 16), although others report a comparable (13) or even higher rate of IVF/ICSI (28). This high proportion of IVF/ICSI pregnancies may be related to the reimbursement of IVF-treatment in Belgium. Up to 6 cycles are covered by the healthcare system, which lowers the barrier to start fertility treatment. In return, the number of embryo's transferred is strictly regulated in favor of a single embryo transfer. In 2017, 5% of all pregnancies in Belgium resulted from IVF/ICSI and 23% of multiple pregnancies (40). We therefore believe the rate of IVF/ICSI pregnancies in our cohort to be representative of the practice in our country.

As a conclusion, patients embarking on a trajectory of IVF/ICSI should be informed that IVF/ICSI increases the chances of conceiving a monochorionic pregnancy, even after single embryo transfer, and that these twins may carry an even higher risk of loss compared to those conceived spontaneously.

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TABLE I: Outcome of monochorionic diamniotic twin pregnancies after in vitro fertilization or intracytoplasmic sperm injection and spontaneous conception

	IVF/ICSI	SPONTANEOUS	P-value	OR [95% CI]	aOR[§] [95% CI]
FETAL LEVEL	**N = 160**	**N = 1148**			
Survival	126/160 (79%)	1031/1148 (90%)	0.001	0.42 [0.25-0.71]	0.42 [0.24-0.74]
Intra-uterine fetal demise	16/160 (10%)	76/1148 (7%)	0.157	1.57 [0.84-2.92]	1.41 [0.72-2.76]
Neonatal death	4/160 (3%)	10/1148 (1%)	0.087	2.92 [0.86-9.94]	2.99 [1.06-8.42]
Major congenital anomaly	10/160 (6%)	57/1148 (5%)	0.484	1.28 [0.64-2.53]	1.14 [0.56-2.31]
PREGNANCY LEVEL	**N = 80**	**N = 574**			
Loss of 1 or both twins	23/80 (29%)	80/574 (14%)	0.001	2.49 [1.45-4.27]	2.48 [1.40-4.38]
Miscarriage	6/80 (8%)	8/574 (1%)[a]	0.002	5.74 [1.94-16.99]	7.23 [2.14-24.39]
Termination of pregnancy	2/80 (3%)[b]	9/574 (2%)[c]	0.547	1.61 [0.34-7.59]	2.00 [0.39-10.38]
Number of survivors					
- 2 survivors	57/80 (71%)	494/574 (86%)	0.003		
- 1 survivor	12/80 (15%)	43/574 (7%)			
- 0 survivors	11/80 (14%)	37/574 (6%)			
Twin-twin transfusion syndrome	8/80 (10%)	69/574 (12%)	0.600	0.81 [0.38-1.76]	0.77 [0.35-1.72]
Selective intra-uterine growth restriction*	18/80 (23%)	87/571 (15%)	0.101	1.62 [0.91-2.86]	1.50 [0.82-2.72]
Gestational age at birth†	35 ± 3 weeks	35 ± 3 weeks[d]	0.924	-	-
Birth before 32 weeks †	11/70 (16%)	81/540 (15%)	0.875	1.06 [0.53-2.10]	1.00 [0.48-2.06]
Neonatal intensive care admission of one or both†	27/69 (39%)	214/525 (41%)[e]	0.795	0.93 [0.56-1.56]	0.89 [0.52-1.53]
Cesarean section†	43/70 (61%)	319/540 (59%)[e]	0.706	1.10 [0.66-1.84]	0.90 [0.52-1.53]
Weight discordance††	12 ± 13 %	12 ± 10 %[f]	0.815	-	-
Birthweight larger twin††	2244 ± 546 grams	2287 ± 528 grams[g]	0.560	-	-

Birthweight smaller twin††	1992 ± 589 grams	2016 ± 543 grams[g]	0.752	-	-

Variables are expressed as proportion (%) and mean ± standard deviation

IVF/ICSI = in vitro fertilisation/intracytoplasmic sperm injection, OR = odds ratio, CI = confidence interval, aOR = adjusted odds ratio

§ Corrected for maternal age and nulliparity

* Defined as discordance in birth weight of 25% or more or discordance in estimated fetal weight of 20% or more prior to intervention or demise

† calculated in pregnancies with at least 1 liveborn twin after 24 weeks (610 pregnancies: 70 after IVF/ICSI and 540 conceived spontaneously)

†† calculated in pregnancies with both twins liveborn after 24 weeks (561 pregnancies: 60 after IVF/ICSI and 501 conceived spontaneously)

[a] 1 miscarriage after prior intra-uterine fetal demise

[b,c] 2 terminations of pregnancy after prior intra-uterine fetal demise in each group

[d] missing data in 3, [e] in 7, [f] in 5 and [g] in 6 pregnancies