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ORIGINAL ARTICLE

Obstetric perinatal and maternal outcomes of monochorionic diamniotic twins following assisted reproductive techniques. Retrospective observational study

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KEYWORDS
Monochorionic diamniotic twins;
Assisted reproductive techniques;
Multiple pregnancy;
Foetal complications;
Maternal complications

Abstract
Introduction: Multiple and specifically monochorionic diamniotic (MCDA) pregnancies are related to maternal and foetal complications. The aim of this study is to evaluate obstetric and perinatal outcomes of MCDA after assisted reproductive techniques (ART).
Methods: This is a case-control study comparing 23 MCDA twin pregnancies after ART (ART-MCDA) and 75 spontaneous MCDA (sMCDA). Maternal, obstetric, foetal, and perinatal outcomes variables including maternal age, prematurity, TTTS, sIUGR, TAPS, PROM, and neonatal weight were compared.
Results: mean maternal age is higher in the ART-MCDA pregnancies, 38.0 ± .6 (OR = 1.32(1.13–1.53)). Neonates weighing between 1500 and 2500 g are more frequent in the sMCDA group and those weighing >2500 g in the ART group (OR = 0.47(0.22–0.97)). Foetuses born at between 32 and 37 weeks are more frequent in sMCDA pregnancies and those born >37 in the TRA group (OR = 0.27(0.09–0.80)). These differences are lost when we adjust the results by maternal age. There were no differences in maternal, obstetric, or foetal complications.
Conclusions: ART-MCDA are not associated with a higher number of maternal, obstetric or foetal complications if they are adjusted by maternal age. When they are not adjusted by maternal age, there would be better outcomes such as premature and neonatal weight in the ART group.

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PALABRAS CLAVE
Gemelos monocoriales diamnióticos;
Técnicas de reproducción asistida;
Embarazo gemelar;
Complicaciones fetales;
Complicaciones maternas

Resultados obstétricos perinatales y maternales en gemelos monocoriales diamnióticos conseguidos mediante técnicas de reproducción asistida. Estudio observacional retrospectivo

Resumen
Antecedentes: El incremento de las técnicas de reproducción asistida (TRA) ha supuesto un aumento de las gestaciones gemelares en general, pero también de las monocoriales biamnióticas (MCBA), que se asocian a diversas complicaciones maternofetales. Estas complicaciones están bien estudiadas en gestaciones espontáneas, pero no en aquellas conseguidas mediante una TRA.
Objetivo: Comparar la incidencia de complicaciones maternas, fetales, obstétricas y perinatales en gestaciones MCBA conseguidas de forma espontánea frente a aquellas conseguidas mediante TRA.
Materiales y métodos: Estudio de casos-controles retrospectivo. Se han analizado 98 gestaciones gemelares MCBA controladas en la Unidad de Medicina Materno-Fetal del Servicio de Obstetricia del Hospital La Paz de Madrid entre los años 2015 y 2020.
Resultados: La media de edad de las madres de las gestaciones MCBA conseguidas mediante TRA es mayor (OR = 1,32 [1,13-1,53]). Los recién nacidos de peso entre 1.500-2.500 g son más frecuentes en las gestaciones MCBA conseguidas de forma espontánea y los de >2.500 g en las de TRA (OR = 0,47 [0,22−0,97]). Los recién nacidos entre las 32-37 semanas son más frecuentes en las gestaciones gemelares MCBA espontáneas y los recién nacidos de >37 semanas en las de TRA (OR = 0,27 [0,09-0,80]). Cuando estos resultados se ajustan por la edad materna dejan de ser estadísticamente significativos.
Conclusiones: Las TRA no conllevan un aumento de las complicaciones en las gestaciones MCBA cuando se ajustan los resultados por la edad materna. Si no se ajustasen por la edad materna, las gestaciones MCBA conseguidas mediante TRA tendrían mejores resultados, con menos prematuridad y mayor peso del neonato.

Introduction

Over the last years, as a consequence of the increase of assisted reproductive techniques (ART) there has been a rise number of twin pregnancies, especially dichorionic diamniotic pregnancies,[1] but also monochorionic diamniotic (MCDA) pregnancies due to the blast stage embryo transfer, although the majority of the MCDA are still spontaneous pregnancies.[2]

Multiple pregnancies are considered as high-risk pregnancies[3] that are related to maternal complications such as preeclampsia, pregnancy-induced hypertension (PIH), gestational diabetes or intrahepatic cholestasis[4]; and fetal complications such as, threatened preterm labor (TPL), premature rupture of membranes (PROM), prematurity, congenital malformations or abruptio placentae.[4]

MCDA have specific complications due to the presence of vascular anastomoses: twin-to-twin transfusion syndrome (TTTS), anemia-polycythemia sequence (TAPS), selective intrauterine growth restriction (sIUGR) and intrauterine fetal death.[5]

These complications are well known in spontaneous pregnancies but there is not almost information in ART pregnancies and the results of these studies are contradictory. Some of them have not found differences in the incidence of fetal, maternal, obstetric and perinatal complications between spontaneous MCDA (sMCDA) and MCDA after ART (ART-MCDA) pregnancies.[6,7] Other authors have found more prematurity and perinatal complications such as lower birth weight in spontaneous pregnancies.[8] Others had found worst perinatal results such as lower birth weight[9] and more prematurity[9,10] or lower overall survival rates and higher rates of second-trimester miscarriage in ART pregnancies.[11]

The aim of the present study is to compare the incidence of maternal, fetal, obstetric and perinatal complications between sMCDA pregnancies and ART-MCDA pregnancies in our center.

Methods

A single case-control retrospective study was conducted at the Department of Obstetrics in the University Hospital La Paz, a tertiary care referral center in Madrid, Spain, after ethical committee approval. Data were collected from MCDA delivered after 24 weeks of gestation from January 1, 2015 to December 31, 2020 in University Hospital La Paz.

The diagnosis of MCDA pregnancy, as well as the weeks of gestation, were made through the first trimester ultrasound and all pregnancies were referred to our center at 12 weeks of gestation.

23 ART-MCDA were studied. For every case approximately three controls were selected, so in total we evaluated 23 ART-MCDA and 75 sMCDA. Women were classified in two groups: ART-MCDA and sMCDA pregnancies. All ART

pregnancies were achieved by in vitro fertilization with autologous oocytes.

Foetal complications (sIUGR [when one of the fetuses is below a percentile 3 or below a percentile 10 with alteration of the Doppler flow or when there is a disagreement between the estimated weights of the two fetuses of more than 20%], TTTS [if a fetus with oligoamnios appears (column of amniotic fluid <2 cm) and the other present polyhydramnios (column of amniotic fluid >8 or 10 cm if it is less than or greater than 20 weeks of gestation respectively), with discordance in the size of the bladders], TAPS [when one fetus is anemic and another is polycythemic], amniotic fluid discordance, foetal biometry discordance, malformations and death), foetal surgery during pregnancy, maternal complications (PIH [systolic blood pressure > 140 and diastolic blood pressure > 90 after 20 weeks of pregnancy], preeclampsia [PIH with proteinuria > 300 mg/24 h], gestational diabetes and intrahepatic cholestasis, PROM and TPL), neonatal birth weight, Apgar score and foetal acidemia [pH after born <7.20]), prematurity [delivery before 37 weeks of gestation] and route of delivery were studied.

Kolmogorov–Smirnov test was used to verify quantitative variables were normally distributed. Chi-square test was used for qualitative variables and Student's *t* test for independent variables for quantitative variables. A statistically significant difference has been considered when p is less than 0.05 with Fisher's exact test or the likelihood ratio. We have calculated the Odds Ratio (OR) with a 95% confidence interval (CI) for the qualitative variables. Subsequently, a multivariate analysis with logistic regression models was performed with the variables whose p was statistically significant. Statistical analysis of the data was performed using the Statistical Package for the Social Science (SPSS) software version 15 (SPSS Inc., Chicago, IL).

Results

Patient characteristics are shown in Table 1. Women in the ART group were significantly older than those in the spontaneous group (mean 38 versus 33.9 years old, $p < 0.01$). There were no differences in maternal complications such as rates of gestational diabetes, PIH, preeclampsia, intrahepatic cholestasis, TPL or PROM (Table 1).

No differences were observed in foetal complications such as TTTS, sIUGR, TAPS, foetal surgery or foetal death. (Table 1). There were no differences in the delivery route (Table 1).

The birth weight was statistically higher in the ART group ($p = 0.03$). Comparing neonatal outcomes, on the univariate analysis, the OR for prematurity was 0.27 (0.09–0.80), and for birth weight between 1500 and 2500 g was 0.47 (0.22–0.97). After adjustment for maternal age, neither the risk of prematurity nor low birth weight remained significantly.

Discussion

Advanced maternal age is related with a higher number of ART and furthermore with twins' gestations. This study confirms that also ART-MCDA are associated with older women than sMCDA. This result agrees with Trojner et al.[9] and Simoes et al.[8]

This study shows that ART-MCDA are not associated with foetal complications. Other studies show similar results.[6–9] Although there are no published studies on the differences between performing foetal surgery, since it is a very recent technique that is practiced in a few hospitals, we have not found differences between both groups.

Regarding maternal and obstetric complications, we have not found significant differences between both groups, as several authors did.[7–9] Paradoxically, despite the advanced maternal age in the ART-MCDA, there were no more maternal complications such as PIH, preeclampsia or gestational diabetes, which may be due to the tight control that these pregnant women have throughout the entire pregnancy.

Couck et al.[11] have found lower overall survival in ART pregnancies including first-trimester miscarriage. As pregnancies are referred to our center at week 12, we have not been able to study first-trimester miscarriage.

Several studies have not demonstrated an association between the type of delivery in ART-MCDA and sMCDA.[8,9,11] This has also been confirmed in our study. This may be due to the fact that, there were no more maternal or fetal complications in the ART group. Nevertheless, Andrijasevic et al.[7] found more cesarean sections in all ART twin pregnancies (MCDA and DCDA).

Some investigators agree with our findings of a lower incidence of prematurity < 37 in ART-MCDA. However, other authors find more prematurity in ART-MCDA group[8,10] or no differences between both groups.[7,11] Our results could be explained because there were no more maternal or fetal complications in the ART-MCDA group. Boria et al.[10] found higher prematurity in twin pregnancies after oocyte donation.

This study shows that ART-MCDA are associated with higher birth weight adjusting for maternal age. Trojner et al.[9] found similar results, although his results were not adjusted for maternal age. However, our results contradict those published by Simoes et al.[8] where they concluded that there was lower birth weight in ART-MCDA group.

Finally, we found that when we adjusted fetal weight and prematurity for maternal age, there are no differences between sMCDA and ART-MCDA. We can say that maternal age is a confounding factor. However, although the differences are no longer significant, there is a tendency to prematurity and lower fetal weight in the group of sMCDA.

The strength of our study is that both cohorts have similar baseline characteristics, except for the maternal age, that is why we have conducted a multivariate analysis adjusting for maternal age. Our study is a single-center case-control retrospective, and nonrandomized study, so it is subject to confounding bias. In order to minimize the bias, we have tried to collect all the data that could have acted as confounding.

Knowing the sample size is small, comparing with the similar studies published (25 ART-MCDA and 483 sMCDA,[8] 45 ART-MCDA and 438 sMCDA,[9] 76 ART-MCDA and 218 sMCDA[6]), which makes us lose statistical power and not detect differences when there really could be, and assuming that this may bias our study, we must say that the prevalence of pregnancies MCDA is low and even more those achieved through ART.

Table 1 Description of variables, statistical significance and factors associated with spontaneous and ART pregnancies.

Variable	Total, $n=98$	Spontaneous, $n=75$	ART, $n=23$	Signification (p)	Odds Ratio (OR)	CI 95%	Signification (p)
Maternal age	34.9 ± 4.4	33.9 ± 0.5	38.0 ± 0.6	<0.01			
Fetal complications							
IUGR	12 (12.2)	11 (14.7)	1 (4.3)	0.28	0.26	0.32–2.16	0.21
IUGR type I		6 (8.0)	1 (4.3)	–			
IUGR type II		2 (2.7)	0 (0)	–			
IUGR type III		3 (4.0)	0 (0)	–			
TTTS	16 (16.3)	13 (17.3)	3 (13.0)	0.76	0.71	0.18–2.76	0.63
Stage I		1 (1.3)	0 (0)	–			
Stage II		8 (10.7)	2 (8.7)	–			
Stage III		3 (4.0)	1 (4.3)	–			
Stage IV		1 (1.3)	0 (0)	–			
TAPS	1 (1.0)	0 (0)	1 (4.3)	0.23	–	–	–
Amniotic fluid discordance	13 (13.3)	12 (16.0)	1 (4.3)	0.29	0.24	0.03–1.94	0.18
Biometry discordance	13 (13.3)	11 (14.7)	2 (8.7)	0.73	0.55	0.11–2.70	0.46
Fetal surgery	17 (17.3)	13 (17.3)	4 (17.4)	0.45	1.10	0.32–3.83	0.87
Prematurity	33.48 ± 4.45	33.29 ± 0.47	34.09 ± 1.16	0.46	–	–	–
<32 weeks	18 (18.4)	14 (18.7)	4 (17.4)	0.06	0.40	0.10–1.58	0.19
Between 32 and 37 weeks	56 (57.1)	47 (62.7)	9 (39.1)	–	0.27	0.09–0.80	0.02
>37 weeks	24 (24.5)	14 (18.7)	10 (43.5)	–	1	–	–
Maternal complications							
Preeclampsia	5 (5.1)	3 (4.0)	2 (8.7)	0.33	2.29	0.35–14.60	0.38
Pregnancy-induced hypertension	3 (3.1)	3 (4.0)	0 (0)	1	–	–	–
Gestational diabetes	3 (3.1)	2 (2.7)	1 (4.3)	0.56	1.66	0.14–19.17	0.68
Intrahepatic cholestasis	0 (0)	0 (0)	0 (0)	–	–	–	–
Obstetric complications							
Premature rupture membrane	8 (7.2)	7 (9.3)	2 (8.7)	1	0.92	0.18–4.79	0.93
Before 28 weeks		2 (2.7)	2 (8.7)	–			
Between 28 and 32weeks		1 (1.3)	0 (0)	–			
After 32 weeks		4 (5.3)	0 (0)	–			
Preterm labour threatening	8 (8.2)	6 (8.0)	2 (8.7)	1	1.09	0.21–5.84	0.91
Before 28 weeks		2 (2.7)	0 (0)	–			
Between 28 and 32weeks		2 (2.7)	2 (8.7)	–			
After 32 weeks		2 (2.7)	0 (0)	–			
Delivery type				0.64			
Vaginal	43 (43.9)	34 (45.3)	9 (39.1)	–			
Caesarean section	55 (54.7)	41 (54.7)	14 (60.9)	–			

Variable	Total, $n=196$	Spontaneous, $n=150$	ART, $n=46$	Signification (p)	Odds Ratio (OR)	CI 95%	Signification (p)
Fetal complications							
Fetal malformations	22 (11.2)	15 (10.0)	7 (15.2)	0.42	1.61	0.61–4.24	0.33
Fetal death	21 (10.7)	14 (9.3)	7 (15.2)	0.28	1.74	0.66–4.62	0.26
Perinatal complications							
Birth weight				0.03			
<1500 g	16 (8.9)	15 (10.6)	1 (2.6)	–	0.14	0.02–1.16	0.07

Table 1 (*Continued*)

Variable	Total, *n* = 98	Spontaneous, *n* = 75	ART, *n* = 23	Signification (*p*)	Odds Ratio (OR)	CI 95%	Signification (*p*)
Between 1500 and 2500 g	101 (56.1)	83 (58.9)	18 (46.2)	–	0.47	0.22–0.97	0.04
>2500 g	63 (35.0)	43 (30.5)	20 (51.3)	–	–	–	–
Umbilical cord pH				1	1.75	0.20–15.02	0.61
<7.20	7 (4.0)	6 (4.4)	1 (2.6)	–			
Equal or >7.20	168 (96.0)	130 (95.6)	38 (97.4)	–			
Apgar score				0.47	0.37	0.46–3.02	0.35
≤7	10 (5.7)	9 (6.6)	1 (2.7)	–			
>7	165 (94.3)	127 (93.4)	38 (97.4)	–			

Conclusion

ART-MCDA are not associated with worse obstetrical, maternal or fetal outcomes than sMCDA. Although in our study there is a lower prevalence of prematurity and birth weight in the ART group, after adjustment for maternal age, it does not remain significant. We believe that this information is important for counselling patients with ART-MCDA pregnancies.

It would be necessary to carry out new studies, with a larger sample size, which would allow us to corroborate the best perinatal results obtained in MCDA pregnancies after the use of ART.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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