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The impact of chorionicity and type of conception on maternal-neonatal outcome in twin pregnancies

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Summary

Purpose of Investigation: To evaluate the maternal and neonatal outcomes in twin pregnancies according to chorionicity (monochorionic (MC) versus dichorionic (DC) and type of conception [spontaneously conceived (SC) versus assisted reproduction technology (ART)]. *Materials and Methods:* A retrospective study of 196 twin pregnancies admitted to the Department of Gynecology, Obstetrics and Urology of the University of Rome Sapienza, from January 2008 to April 2013. *Results:* There were 55 MC and 141 DC twin pregnancies (82 SC and 59 ART). MC twin pregnancies had a higher incidence of preterm birth ($p < 0.008$), twin-twin transfusion syndrome (TTTS) ($p < 0.021$), and intrauterine growth restriction (IUGR) ($p < 0.05$). MC pregnancies had lower neonatal birth weight ($p < 0.05$), and lower Apgar score. ART DC pregnancies had a higher incidence of preterm delivery ($p < 0.05$). *Conclusions:* MC twin pregnancy is associated with higher risk of adverse maternal and perinatal outcomes. In the DC subgroup, ART is associated to a higher incidence of preterm delivery.

Key words: Twin pregnancy; Assisted reproduction technology; Mode of conception; Chorionicity; Monochorionic; Dichorionic.

Introduction

The rate of multiple pregnancies in developed countries continues to rise as a consequence of assisted conception and increasing maternal age [1]. In the United States, between 1980 and 2007, the twin rate climbed 101% [2]. In Italy, between 1990 and 2005, the number of twin births has increased by 25% and twin gestation today represents 1.5% to 3% of all pregnancies. About 80% of twin pregnancies are dichorionic (DC) and 20% are monochorionic (MC) [3].

Chorionicity is the most important determinant of mortality and morbidity in twins. Most studies confirmed higher risks for MC compared with DC pregnancies in relation to perinatal outcomes [4, 5]. Indeed, the main risks for MC twins are the twin-twin transfusion syndrome (TTTS) (15%) [6] and prematurity (50%) [7]. However, the recent rise in twin pregnancies results mainly from a greater proportion of DC pregnancies, that is largely explained by the increasing use of assisted reproduction technology (ART). In the USA and Europe between 20% and 30% of deliveries following ART are twins, compared with approximately 1% following spontaneous conception (SC) [8]. In Caucasian populations, about 22% of SC twins are MC, whereas this rate falls to about 2% in ART [9]. Literature data concerning the influence of ART on the outcome of twin pregnancies are controversial.

The purpose of this study was to evaluate the maternal and neonatal outcomes in multiple pregnancies, according to two different parameters, namely chorionicity (MC versus DC) and mode of conception (SC versus ART).

Materials and Methods

The authors performed a retrospective analysis of the multiple pregnancies that delivered at the Department of Gynecology, Obstetrics and Urology of the University of Rome Sapienza, from January 2008 to April 2013. Exclusion criteria were gestational age (GA) less than 24 weeks at delivery and early or late miscarriages.

The authors acquired the details of the pregnancies and deliveries from the medical records. In particular, they collected demographic data, relevant past history, parity, mode of conception (SC versus ART), chorionicity (MC versus DC), GA at admission and at delivery, time of maternal hospital stay ante- and post-partum, pregnancy outcomes, and maternal-fetal complications, therapy during gestation, short-term neonatal outcomes.

The chorionicity was determined at 10-14 weeks on the basis of the presence or absence of the lambda sign or a projection of choriodecidual tissue into the inter twin membrane. Gestational age was calculated from the last menstrual period and confirmed, or corrected, by means of ultrasounds examination through the measurement of the crown-rump length.

The authors recorded the following maternal-fetal complications: preterm delivery, threatened preterm labour, preterm premature rupture of membranes (pPROM), intrauterine growth restriction (IUGR), TTTS according to Quintero's criteria [10], and selective IUGR, pregnancy induced hypertension (PIH), preeclampsia (PE), hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) syndrome, gestational diabetes mel-

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litus (GDM), cholestasis, oligohydramnios, polyhydramnios, abnormal placentation, placental abruption, and intrauterine death (IUD).

With regards to short-term neonatal outcome, the authors collected the following parameters: birth weight and related percentile according to classification proposed by Parazzini *et al.* [11], Apgar score at one and five minutes, and the discordance of twin weight. Discordance was calculated by using the following formula: larger twin – smaller birth weight x 100/larger twin birth weight.

Patients were grouped according to chorionicity (MC *vs* DC) and the mode of conception (SC *vs* ART), to evaluate the impact of these variables. The data were analyzed with SPSS 16.5 Windows program. Comparisons between the two groups were performed with the Student's *t*-test and chi-square test. Significance was assumed at $p < 0.05$.

Results

The authors collected 196 twin pregnancies, further subgrouped into 55 MC and 141 DC. The MC subgroup included 49 SC pregnancies (89.1%) and six conceived by ART (10.9%). In particular, three pregnancies were obtained by intracytoplasmic sperm injection (ICSI), one pregnancy by fertilization in vitro and embryo transfer (IVF-ET), and two pregnancies after intrauterine insemination (IUI). The DC subgroup included 82 SC pregnancies (58.2%) and 59 conceived by ART (41.8%). In particular, 35 pregnancies were obtained by ICSI, 21 pregnancies by IVF-ET, and three pregnancies by IUI. The authors considered only the 36 DC pregnancies obtained by IVF, namely IVF-ET and ICSI, after ovulation induction in order to compare SC versus ART twin pregnancies.

MC versus DC pregnancies

The authors compared 55 MC versus 141 DC pregnancies. Maternal age, parity, duration of ante and post-partum hospital stay, and type of delivery, were not significantly different between subgroups.

With regards to the mode of conception, the rate of conception by ART was significantly higher in the DC subgroup (41.8% *vs* 10.9%; $p < 0.05$). GA at admission was approximately two weeks earlier in MC pregnancies (33 ± 3 *vs* 35 ± 2.7 weeks, $p < 0.05$).

The incidence of abnormal placentation, placental abruption, IUD, PIH, PE, HELLP syndrome, cholestasis, and GDM was not significantly different between the two subgroups. The MC subgroup had a higher incidence of threatened preterm delivery (58.2% *vs* 32.6%, $p = 0.001$) [OR= 2.87, 95% 1.51 - 5.46], and pPROM (31% *vs* 13.5%, $p = 0.007$) [OR= 2.87, 95% 1.36 - 6.07]. Moreover, 7.2% of MC pregnancies were complicated by TTTS, while this complication never occurred in the DC subgroup ($p < 0.05$). No case of TTTS was treated with laser therapy prior to delivery.

GA at delivery was on average one week earlier in MC group than DC group (34±3 *vs* 35.5 ± 2.3 weeks). In particular, 85.5% of MC delivered before 37 weeks, as compared to 66.7% in the DC subgroup ($p < 0.05$) [OR= 2.94, 95% CI 1.28 - 6.72].

In the MC subgroup, IUGR occurred in 28% of cases, as compared to 12% in the DC subgroup ($p < 0.05$), though the difference of incidence of selective IUGR did not reach statistically significance. In MC pregnancies, lower neonatal birth weight were found (1,990 ± 526 *vs* 2,246 ± 473 grams,

Table 1. — *Comparison between MC and DC pregnancies.*

Variables	MC group (n=55)	DC group (n=141)	*p*
Characteristics of patients			
Maternal age (years) (mean ± SD)	32 ± 6	32.6 ± 5.3	NS
Parity			
0	41 (74.5%)	104 (73.7%)	NS
≥1	14 (25.5%)	37 (26.3%)	NS
ART pregnancies	6 (10.9%)	59 (41.8%)	<0.05
SC pregnancies	49(89.1%)	82(58.2%)	<0.05
Length of hospital stay			
Ante-partum stay (days) (mean ± SD)	6 ± 11	4 ± 8	NS
Post-partum stay (days) (mean ± SD)	4 ± 2	4 ± 2	NS
Mode of delivery			
Vaginal delivery	3 (5.5%)	5 (3.5%)	NS
Cesarean section	52 (94.5%)	136 (96.5%)	NS
Short-term neonatal outcome			
Birthweight (grams) (mean ± SD)	1,990 ± 526	2,246 ± 473	<0.05
Birthweight percentile	38.7 ± 26	46.4 ± 23.7	<0.05
Apgar 1 minute ≤7	40%	29.8%	<0.05
Apgar 5 minutes ≤7	2.7%	4.2%	NS
Discordance of birthweight	14.7%	11.7%	NS
IUD	5.4%	1.4%	NS
Pregnancy outcome			
pPROM	31%	13.5%	<0.05
Threatened preterm delivery	58.2%	32.6%	<0.05
Delivery < 37 weeks	85.5%	66.7%	<0.05
Abnormal placentation	1.8%	1.4%	NS
Placental abruption	3.6%	1.4%	NS
Polyhydramnios	0%	0.7%	NS
Oligohydramnios	11%	6.4%	NS
IUGR	28%	12%	<0.05
Selective IUGR	11%	5.7%	NS
PE/HELLP	5.59%	7.8%	NS
PIH	3.6%	12.8%	NS
Cholestasis	3.6%	11.3%	NS
GDM	3.6%	1.4%	NS
TTTS	7.2%	0%	<0.05

Table 2. — *Comparison between spontaneous and ART pregnancies.*

Variables	SC group (n=82)	ART group (n=56)	*p*
Characteristics of patients			
Maternal age (years) (mean ± SD)	33±5	32.4±5.4	NS
Parity			
0	48 (58.5%)	53 (94.6%)	P<0.05
≥1	34 (41.5%)	3 (5.4%)	P<0.05
Ante-partum stay (days) (mean ± SD)	4 ± 9	4 ± 6	NS
Post-partum stay (days) (mean ± SD)	4 ± 2	5 ± 2.6	NS
Mode of delivery			
Spontaneous delivery	4 (5%)	1 (1.8%)	NS
Cesarean section	78 (95%)	55 (98.2%)	NS
Neonatal outcome			
Birthweight (grams) (mean ± SD)	2,176 ± 523	2,186 ± 456	NS
Percentile	47 ± 24	45.5 ± 23	NS
Apgar 1 minute ≤7	30%	30.5%	NS
Apgar 5 minutes ≤7	3.6%	5.3%	NS
IUD	3.7%	0%	NS
Pregnancy outcome			
pPROM	12.2%	16.1%	NS
Threatened preterm delivery	29.3%	37.5%	NS
Delivery < 37 weeks	61%	76.8%	<0.05
Abnormal Placentation	1.2%	1.8%	NS
Placental abruption	3.6%	1.4%	NS
Polyhydramnios	1.2%	0%	NS
Oligohydramnios	8.5%	3.6%	NS
IUGR	11%	13%	NS
Selective IUGR	4.9%	7.1%	NS
PE/HELLP	6.1%	10.7%	NS
PIH	12.2%	14.3%	NS
Cholestasis	11%	12.5%	NS
GDM	1.2%	3.6%	NS
TTTS	0%	0%	NS

$p < 0.05$), as well as lower birth weight percentile (38.7 ± 26 *vs* 46.4 ± 23.7, $p < 0.05$), and larger discordance of twin weight (14.7 ± 10.6% *vs* 11.7 ± 8.4%, $p > 0.05$). Additionally, Apgar score ≤ 7 at one minute was found in 40% of MC, as compared to 29.8% of DC ($p < 0.05$), though the rate of Apgar score ≤ 7 at five minutes was similar in the two subgroups (Table 1).

With regards to the drug treatments, there were no statistically significant differences between the two groups, except for a greater use of antenatal corticosteroid therapy in the MC subgroup (38.2% *vs* 26.2%, $p < 0.05$).

DC twin pregnancies conceived by ART versus SC

The authors compared 56 DC pregnancies conceived by ART (IVF-ET/ICSI) and 82 DC pregnancies conceived spontaneously. Maternal age, duration of ante and post-partum stay, type of delivery, birth weight, and short-term neonatal outcome were not significantly different between subgroups. Parity in the ART subgroup was 0.05 ± 0.22, and 0.41 ± 0.49 in the SC group ($p < 0.05$).

The incidence of abnormal placentation, placental abruption, IUD, PIH, PE, HELLP syndrome, cholestasis, GDM, and IUGR was not significantly different between the two subgroups.

The ART pregnancies showed a higher incidence of preterm delivery before 37 weeks (76.8% *vs* 61.0%, $p < 0.05$) (Table 2).

Additionally, women in the ART subgroup received more frequently drug treatments, in particular low-molecular-weight heparin LMWH (50.0% *vs* 22.0%, $p = 0.001$), cardioaspirin (23.2% *vs* 6.1%, $p = 0.005$), and prednisone (14.3% *vs* 0%; $p = 0.001$), as well as the administration of progesterone (30.4% *vs* 12.2%, $p = 0.01$). Similarly, the antenatal corticosteroid therapy with betamethasone was administered more frequently in the ART subgroup (35.7% *vs* 19.5%, $p = 0.01$).

Discussion

Twin pregnancy is burdened by a higher risk of adverse outcomes compared with singleton. This issue is becoming more frequent in clinical practice, and subsequently topical in clinical literature, due to the dramatic increase of the incidence of multiple births in the developed countries over the past decades.

Most studies showed a higher incidence of preterm births and adverse neonatal outcomes in MC pregnancies, possibly related to TTTS and selective IUGR [5, 7]. According to Acosta-Rojas *et al.*, the adverse perinatal outcomes of MC twins appear to be associated with selective IUGR [6].

In accordance with literature data, the present study found that in the MC subgroup GA at admission was one week earlier than DC, likely related to the higher incidence of pPROM, preterm births, IUGR, and TTTS. However, the present data confirmed the greater incidence of selective IUGR, though not statistically significant in MC pregnancies. Additionally, the present authors found a higher incidence of adverse short-term neonatal outcomes in the MC subgroup, as fairly expected.

Literature data concerning the maternal complications are controversial [7, 12, 13]. The present study did not disclose any difference between MC and DC twin pregnancies. Hypertensive disorders were more frequently associated to DC pregnancy, though this evidence was not statistically significant. Nonetheless, a limitation of the present study may be represented by the low number of MC pregnancies.

The present study further investigated the impact of ART on the outcome of DC pregnancies. ART has been related to a higher risk of maternal-fetal complications and preterm birth in some studies, that compare the outcomes of singleton pregnancies conceived by ART with those conceived spontaneously [14-17]. On the contrary, several studies investigating the outcome of twin pregnancies conceived by ART have produced conflicting results [14, 18-27].

Interestingly, a recent meta-analysis of perinatal risks in twins, which selected studies that matched or controlled for maternal age and others factors, showed that ART twins had an increased risk of preterm birth and low birth weight compared to SC twins [28]. However, this meta-analysis was not adjusted for chorionicity, albeit this is an important prognostic factor in both ART and SC twin pregnancies.

In the present study, the authors restricted their analysis of the impact of ART to the DC subgroup in order to avoid the bias of monochorionicity. Other studies carried out this analysis after controlling for chorionicity or zygosity but their results are inconsistent [24, 29]. Furthermore, maternal age is supposed to be an additional variable eventually affecting the outcome of ART twin pregnancies. In fact, women delivering after ART are often older than the average population of pregnant women and almost always nulliparae, and this fact has often been used to explain the adverse obstetric and perinatal outcomes observed in these patients.

In the present study, the authors found lower parity in the ART women, as fairly expected. Interestingly, the maternal age (ART versus SC) was similar in the two subgroups, thus reducing the influence of this variable. Thus, the present findings may be considered controlled for chorionicity, due to methodological limitations, and for maternal age, by chance. Actually, the outcomes of ART twin pregnancies were generally comparable with SC twin pregnancies, except for a higher incidence of preterm delivery and a related use of antenatal corticosteroid therapy.

In the literature, the increased risk of preterm birth has been suggested to be secondary to higher concentrations of relaxin throughout gestation following gonadotropin stimulation [30]. Another factor that may contribute to higher rates of preterm birth is the increased rate of obstetric intervention, since ART birth is often the first birth after a history of infertility, so that both the physician and mother may be more worried about delivery than in SC pregnancies [31]. With regards to maternal complications, most studies do not find any statistically significant difference between ART and SC twin pregnancies [15, 19, 23, 25]. A higher prevalence of GDM in the ART group, possibly explained by the high rate in ART group of women suffering from polycystic ovary syndrome, which is associated with insulin resistance, has been anecdotally reported [21]. Additionally, a higher incidence of pPROM in the ART group, eventually affecting a higher rate of prematurity, has been suggested [20]. Higher rates of placenta previa and placental abruption occur more frequently in the ART group. This could be a consequence of embryo transfer through the vagina and cervix, as well as defective uteroplacental interactions related to female fertility problems [14, 27]. Finally, a higher percentage PIH has been hypothesized to be eventually explained by the different initiation of the chorion formation while the embryo is in vitro, leading to an abnormal placentation in both location and function [18].

A recent review about ART twin pregnancies reported increased obstetrical risks only in women with a pre-existing medical condition such as hypertensive disorders or diabetes [32], albeit most of these risks can be avoided with single-embryo transfer or with two single-embryo transfers resulting in two singleton pregnancies [33].

In the present study, the incidence of maternal complications was not significantly different between SC and ART subgroups. It is worth to note that in the ART subgroup there was a greater use of drugs, in particular LMWH, cardioaspirin, and prednisone. The impact of this medical therapy on preventing maternal complications, in particular the hypertensive disorders, is far from being understood.

Conclusion

The present study did not disclose any significant difference in the short-term neonatal outcomes between SC and ART DC twins. MC twin pregnancy was associated with higher risk of adverse outcomes compared with DC pregnancy, as previously reported. In particular, a higher incidence of TTTS, IUGR, preterm birth, a related more frequent use of antenatal corticosteroid therapy, and worse short-term neonatal outcome were noticed. Moreover, the present analysis of DC twin pregnancies suggests that ART is possibly related to a higher incidence of preterm delivery and a related use of antenatal corticosteroid therapy if compared to SC twin pregnancies.

Further studies are advocated to confirm the present findings and investigate possible difference in neonatal morbidity (incidence of respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, etc).

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