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Obstetric and perinatal outcomes in twin pregnancies conceived through assisted reproduction: A retrospective cohort study

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ABSTRACT

Introduction. Multiple pregnancies are more frequently associated with adverse maternal and neonatal outcomes. The incidence of multiple pregnancies has increased with the use of assisted reproductive technologies (ART): they account for between 15% and 25% of twin births. ART has also been associated with adverse outcomes in both singleton and multiple pregnancies, although the available evidence is limited and heterogeneous.

Objective. To evaluate maternal and perinatal outcomes in spontaneously conceived twin pregnancies and compare them with those conceived through ART.

Population and methods. Patients aged 18 years or older with twin pregnancies who reached a gestational age of 24.0 weeks and who underwent first-trimester screening, follow-up, and delivery at the Hospital Italiano de Buenos Aires between January 2014 and December 2022. A composite outcome of maternal and neonatal adverse events was analyzed. Neurological development was monitored until age 2.

Results. A total of 243 twin pregnancies were included (148 ART; 95 spontaneous). The ART group had a higher prevalence of advanced maternal age, nulliparity, obesity, and chronic diseases, with statistically significant differences (p <0.001). There were no significant differences in primary maternal outcomes (29% vs. 23%; p = 0.347) or neonatal outcomes (16% vs. 19%; p = 0.371). We found an increased frequency of autism spectrum disorders in pregnancies conceived through ART.

Conclusion. Twin pregnancies resulting from ART showed similar maternal and neonatal outcomes to those resulting from spontaneous conception, despite significant differences in baseline maternal characteristics. Long-term follow-up studies are needed.

Keywords: *multiple pregnancy;* in vitro *fertilization; perinatology; morbidity; preterm labor.*

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INTRODUCTION

Twin pregnancies are considered high-risk, as they carry a significantly higher risk of adverse maternal and perinatal outcomes compared to singleton pregnancies.[1,2] Fetal and neonatal complications include increased fetal mortality,[3] preterm birth, low birth weight, and a higher rate of admission to the neonatal intensive care unit (NICU).[3,4-6]

The incidence of multiple pregnancies has increased significantly with the advent of assisted reproductive technologies (ART). It is estimated that these account for between 15% and 25% of all twin births.[7,8] In Argentina, approximately 0.6% of newborns result from fertility treatments, compared to 2.6% reported in the United States for 2022.[9] There are no data on multiple pregnancies.[10]

Various social changes are modifying patterns of human reproduction: a declining birth rate[11] and a delay in the age at which women seek to become pregnant, leading to an increase in the use of ART. Older women with more preexisting chronic conditions and a higher risk of adverse pregnancy outcomes characterize this new epidemiological landscape.[12,13]

In both singleton[14] and multiple[15] pregnancies, ARTs have been associated with an increased risk of adverse outcomes. However, published systematic reviews and meta-analyses include few studies with imprecise risk estimates and include cohorts with high-order multiple pregnancies (three or more).[14,16]

This study aims to compare the outcomes of twin pregnancies conceived through ART with those of spontaneously conceived (SC) twin pregnancies, to determine whether the former carry additional risks.

POPULATION AND METHODS

A retrospective cohort study was conducted among patients aged 18 or older with twin pregnancies who reached 24.0 weeks' gestation and underwent first-trimester screening, follow-up, and delivery at the Hospital Italiano de Buenos Aires between January 2014 and December 2022. The patients in the ART group came from multiple fertility centers; therefore, the data reflect standard practices of those centers, rather than those of any particular institution.

The cohort was assembled using data from the first-trimester survey and the birth registry database. To evaluate the results of the cohort analysis, exposure was defined as pregnancy achieved through assisted reproductive technology, and the frequency of adverse outcomes was compared with a concurrent unexposed cohort of SC twin pregnancies, which served as the control group. Maternal and neonatal data were obtained from electronic medical records.

The following data were recorded for each pregnant woman: age, weight, height, mode of conception, ultrasound measurements (11-14 weeks), obstetric history, pre-existing medical conditions, mode and onset of labor, and complications during pregnancy and the postpartum period. For the ART group, the cause and type of treatment performed were recorded, ranging from ovulation induction to ICSI with egg donation. Gestational age and chorionicity were confirmed by first-trimester ultrasound.

The perinatal data collected included birth weight, sex, Apgar score, congenital anomalies, admission to the NICU, neonatal and perinatal mortality rates, the frequency and type of newborn complications, weight discrepancy between twins, and length of hospital stay.

To measure the incidence of a composite primary outcome, the severe maternal morbidity index (SMMI) was used, which consisted of the presence of one or more of the following complications: preeclampsia, chorioamnionitis, *placental abruption*, postpartum hemorrhage, need for transfusions, need for hysterectomy, respiratory failure, renal failure, myocardial infarction, and stroke.[17]

The incidence of obstetric complications was measured using the obstetric morbidity index (OMI), which is defined by the presence of any of the following outcomes: antepartum hemorrhage, preeclampsia, preterm premature rupture of membranes, gestational diabetes, fetal growth restriction, need for hospitalization during pregnancy, postpartum hemorrhage, need for transfusions, need for secondary interventions in the postpartum period (placement of a hemostatic balloon, uterine artery embolization, hysterectomy).

The frequency of a composite outcome of neonatal adverse events (neonatal morbidity index, NMI) was also analyzed; this outcome consisted of the presence of one or more of the following: admission to the NICU, small for gestational age (SGA), preterm birth, severe neonatal depression, periventricular leukomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, grade II

or higher periventricular hemorrhage, necrotizing enterocolitis, confirmed sepsis before discharge, fetal death or neonatal death, or congenital malformations.[18]

Secondary outcomes included each of the components of the primary maternal and neonatal outcomes individually, discordance in size and weight at birth, and method of pregnancy termination.

The newborns were identified and followed up through electronic records. Neurodevelopmental disorders were recorded (autism spectrum disorders, pervasive developmental disorders, attention-deficit/hyperactivity disorder, and language and learning disorders). Cases with at least 2 years of follow-up are reported. Neurocognitive development was assessed using a variety of individualized tools tailored to the patient's history and clinical presentation, as determined by the pediatric follow-up team. The diagnoses of the various disorders were recorded by pediatric specialists in their respective fields when made. A descriptive analysis of the data was performed using measures of central tendency and dispersion as appropriate. The chi-square test or Fisher's exact test was used to compare categorical variables. Continuous variables were analyzed using parametric or nonparametric tests as appropriate. Associations are reported as odds ratios (OR) and their corresponding 95% confidence intervals (95%CI). A univariate logistic regression analysis was performed to describe the relationship between the dependent variable (primary maternal and neonatal outcomes) and a group of independent variables. Subsequently, variables associated with the primary outcome (p <0.1) were included in a multivariate regression model along with variables considered important *a priori*, for clinical reasons.

A generalized linear model was used to assess neonatal outcomes, accounting for the correlation between pairs of newborns from the same mother.

The data collected were entered into an anonymous computerized database and analyzed using STATA 17 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845, USA).

The study was approved by the Research Protocol Ethics Committee (CEPI) of the Hospital Italiano de Buenos Aires under number 6001.

RESULTS

During the study period from 2014 to 2022, 243 twin pregnancies were included (148 achieved through assisted reproductive technology and 95 conceived spontaneously).

Maternal age (37.8 ± 4.9 vs. 34.4 ± 5.2; p < 0.001), weight (69.5 ± 13.5 kg vs. 65.2 ± 13.9; p <0.016), body mass index (26.6 ± 5.2 kg vs. 24.9 ± 4.8; p = 0.009), history of chronic diseases (45% vs. 25%, OR 2.4, 95% CI 1.3-4.5; p = 0.002), obesity (23% vs. 12%, OR 2.6, 95% CI 1.1-6.2; p = 0.026), and nulliparity (88% vs. 59%, OR 5.3, 95% CI 2.6-10.9; p <0.001) were significantly higher in the ART conception group (*Table 1*). As expected, the frequency of monochorionic twin pregnancies was significantly higher in spontaneously conceived pregnancies (6% vs. 36%, p <0.001) (*Table 2*).

Obstetric complications and delivery outcomes among twin pregnancies with and without ART are described in *Table 2*. We observed no significant differences in the primary outcome, SMMI, between women conceived through ART and those conceived spontaneously (30% vs. 24%, OR 1.3, 95% CI 0.7-2.5; p = 0.347), nor in the IMO (67% vs. 54%, OR 1.5, 95% CI 0.8-2.7, p = 0.113). There were also no significant differences in any of the individual obstetric outcomes.

The primary neonatal composite outcome (NMI) (16% vs. 19%, p = 0.371) also showed no significant differences between the groups. Perinatal outcomes are described in *Table 3*. Gestational age at birth (35 ± 2 vs. 35 ± 3, p = 0.885), birth weight (2293 ± 594 vs. 2209 ± 479, p = 0.104), and an Apgar score <7 at 5 minutes (1% vs. 2%, p = 0.324) were similar in both groups.

There was a total of 11 perinatal deaths. Six fetal deaths, 4 in the ART group and 2 in the SC group (1.3% vs. 1%, p = 0.77); and 5 neonatal deaths in the ART group (5% vs. 0%, p = 0.07).

Among pregnancies resulting from ART and spontaneous conceptions, there were 37 and 17 newborns with malformations, respectively (13% vs. 9%, p = 0.148). Cardiovascular malformations were the most common (14 and 8, respectively), followed by central nervous system anomalies (9 and 1), and urogenital malformations (5 and 2). Perinatal outcomes are described in *Table 3*. After adjusting for baseline differences in maternal age, nulliparity, abortions, body mass index, obesity, chronic diseases, chorionicity, and adnexal surgeries, regression analysis revealed that there were no significant differences between the two groups (p >0.05) in terms of maternal and obstetric morbidity rates.

A subanalysis was conducted comparing pregnancies resulting from highly complex

Table 1. Clinical characteristics of the population

	ART conception (n = 148)		Spontaneous conception (n = 95)		
	n	%	n	%	*p*
Maternal age at delivery					
>35 years	115	(78)	50	(53)	<0.0001
>40 years	50	(34)	10	(10)	<0.0001
>45 years	15	(10)	0	(0)	0.001
Primigravida	108	(73)	50	(53)	0.001
Nulliparous*	131	(88)	56	(59)	<0.0001
Miscarriages*	24	(60)	18	(40)	0.066
Vaginal deliveries#	5	(29)	18	(46)	0.242
Previous cesarean sections#	12	(71)	21	(54)	0.242
Chronic disease@	67	(45)	24	(25)	0.002
Severe chronic disease&	18	(12)	7	(7)	0.230
Obesity	34	(23)	11	(12)	0.026
Pregestational diabetes	3	(2)	1	(1)	0.560
Chronic hypertension	4	(3)	0	(0)	0.106
Kidney disease	0	(0)	0	(0)	-
Autoimmune disease	0	(0)	2	(2)	0.076
Thrombophilia	7	(5)	2	(2)	0.290
Hypothyroidism	27	(18)	10	(10)	0.102
Smoking	5	(3)	1	(1)	0.254
Epilepsy or CNS disorder	1	(0.7)	3	(3)	0.138
Cervical resection procedures	1	(0.6)	2	(2)	0.325
Endometriosis	4	(3)	0	(0)	0.106
Myomatosis	3	(2)	0	(0)	0.163
Myomectomy	3	(2)	0	(0)	0.163
Adnexal surgeries	25	(17)	0	(0)	<0.0001
Chorionicity					
Bichorial	139	(97)	61	(64)	
Monochorial	9	(6)	34	(36)	<0.0001

@ Excludes endometriosis.
& Chronic hypertension, kidney disease, autoimmune disease, thrombophilia, pregestational diabetes, uterine fibroids, uterine abnormalities, and cervical surgery.
** Among women who have been pregnant.*
 # Among women who have given birth.
CNS: central nervous system.

techniques (techniques requiring egg retrieval and incubation: conventional *in vitro* fertilization and ICSI) with those resulting from spontaneous conception, yielding similar results (*Supplementary Material: Table C.2 Obstetric Outcomes, Table C.3 Neonatal Outcomes*).

In the cohort of newborns with at least 2 years of follow-up, 65 children were found to have neurodevelopmental disorders, 45/280 (16%) in the ART group and 20/178 (11%) in the spontaneous conception group (p <0.001) (*Table 4*).

DISCUSSION

In this retrospective cohort study of 243 twin pregnancies, no significant differences were observed in maternal and perinatal outcomes between pregnancies conceived through ART and those conceived spontaneously. Although women in the ART group had a significantly higher maternal age, increased prevalence of nulliparity, obesity, and chronic diseases, these factors did not result in increased severe maternal morbidity or adverse neonatal outcomes. However, we found a higher frequency of neurodevelopmental disorders in the ART-conceived group, primarily due to autism spectrum disorders (ASD).

The existing literature yields mixed results. Our findings are consistent with several previous studies that have also found no significant differences in obstetric and perinatal outcomes

Table 2. Comparison of obstetric outcomes between twin pregnancies conceived through ART and those conceived spontaneously

	ART conception (n = 148)		Spontaneous conception (n = 95)				
	n	%	n	%	OR	95%CI	*p*
SMMI	44	(28)	23	(24)	1.38	0.73-2.3	0.347
OMI	99	(67)	54	(57)	1.53	0.87-2.7	0.114
Preterm birth <32 weeks	14	(11)	10	(11)	1.21	0.46-3.1	0.696
Preterm birth <34 weeks	19	(15)	16	(17)	0.99	0.51-1.9	0.996
Preterm birth <37 weeks	83	(66)	70	(74)	0.67	0.37-1.1	0.183
Preeclampsia	30	(24)	16	(17)	1.47	0.76-2.8	0.250
Preeclampsia <34 weeks	7	(23)	2	(12)	2.15	0.40-11	0.371
Gestational diabetes	22	(18)	9	(9)	1.84	0.82-4.1	0.139
Antepartum hemorrhage	6	(4)	1	(1)	3.97	0.47-33	0.205
TPL	29	(23)	12	(13)	2.30	1.13-4.6	0.021
PPROM	9	(7)	12	(13)	0.61	0.26-1.4	0.252
Chorioamnionitis	2	(2)	2	(2)	0.63	0.08-4.6	0.655
Cholestasis	10	(8)	7	(7)	1.10	0.42-2.9	0.834
Hospitalization during pregnancy	34	(27)	24	(25)	1.02	0.56-1.8	0.943
FGR[++]	27	(21)	11	(12)	1.70	0.80-3.6	0.166
Admission to the ICU	4	(3)	5	(5)	0.50	0.13-1.9	0.311
Postpartum hemorrhage	5	(4)	3	(3)	1.29	0.31-5.3	0.719
Secondary interventions	2	(1)	3	(3)	0.42	0.06-2.5	0.347

SMMI: severe maternal morbidity and mortality index, OMI: obstetric morbidity index, TPL: threatened preterm labor, PPROM: preterm premature rupture of membranes, FGR: fetal growth restriction, ICU: intensive care unit.

[++] *Calculated as a pregnancy diagnosis.*

between multiple pregnancies conceived through ART and those conceived naturally.[19-22] However, other publications indicate an increased risk of adverse outcomes in ART twin pregnancies, including preterm birth, preeclampsia, gestational diabetes, congenital malformations, higher rates of admission to the neonatal intensive care unit, and weight discordance.[16,23,24] However, the reported maternal and neonatal outcomes show significant heterogeneity, which could be explained by varying methodological quality of the studies, selection biases, inclusion or exclusion of women with comorbidities, differences in clinical management, and differences in outcome definitions.[24]

The implementation of a standardized follow-up program at our center could partly explain the discrepancy between our findings and those of studies reporting worse outcomes. Close monitoring, specialized prenatal care, and multidisciplinary management of twin pregnancies (particularly those achieved through ART) could help mitigate the risks associated with these pregnancies.

According to data from the World Health Organization, up to 6% of newborns have a congenital malformation;[25,26] in multiple pregnancies, this figure doubles, with wide variations between studies attributable to differences in the definitions and inclusion criteria for anomalies.[27] In our population, which is mainly dichorionic twins, consistent with the findings reported by Vasario *et al.*,[19] the prevalence of anomalies is high. Although selection bias is a possibility, twin pregnancies referred late in the pregnancy are not included, as enrollment occurred during the first-trimester screening. Another possible explanation is that this is not strictly a prevalence at birth, as some children have been followed for up to 10 years. Regardless of the differences found, the maternal age in both groups is significantly higher than that of the general population, which is associated with a higher frequency of congenital anomalies.[28]

Regarding the increasing prevalence of ASD, our findings are consistent with the meta-analysis by Andreadou *et al.*,[29] however, other studies report conflicting results, attributing

Table 3. Comparison of perinatal outcomes between twin pregnancies conceived through ART and spontaneously

	ART conception (n = 296)		Spontaneous conception (n = 95)				
	n	%	n	%	OR	95%CI	*p*
Severe neonatal morbidity index[#]	47	(16)	36	(19)	0.84	0.14–1.6	0.244
Apgar <7 at 5 minutes[+]	3	(1)	4	(2)	0.66	0.81–5.4	0.701
LBW <10th percentile[++]	31	(11)	30	(16)	0.67	0.40–1.1	0.150
LBW <3rd percentile[++]	13	(4)	10	(5)	0.87	0.35–2.1	0.777
Discordance >25%	25	(17)	9	(10)	2.21	0.95–5.1	0.065
CRL discordance >10%	24	(16)	11	(12)	1.75	0.77–3.9	0.176
Congenital malformation	37	(13)	17	(9)	2.03	0.77–5.3	0.149
Admission to NICU*	146	(50)	109	(58)	0.39	0.10–1.5	0.179
Hyaline membrane disease	45	(15)	32	(17)	0.76	0.18–3.1	0.711
Transient tachypnea	48	(16	39	(21	0.61	0.25–1.4	0.282
Sepsis	6	(2)	2	(1)	2.15	0.22–20.	0.506
Intraventricular hemorrhage III-IV	7	(2)	1	(0.5)	6.29	0.37–10	0.203
Necrotizing enterocolitis	11	(4)	6	(3)	1.29	0.21–7.5	0.780
Hyperbilirubinemia	61	(21)	40	(21)	0.88	0.28–2.7	0.836
Hypoglycemia	12	(4)	5	(3)	1.90	0.42–8.3	0.401
Fetal death	4	(1)	2	(1)	8.05	0.09–67	0.356

[#] Includes any of the following: neonatal death. sepsis, hyaline membrane disease, necrotizing enterocolitis, periventricular leukomalacia, grade III or IV intraventricular hemorrhage, and bronchopulmonary dysplasia.
** Among live births.*
[++] Based on the total number of live births according to Intergrowth, adjusted for sex.
LBW: low birth weight; CRL: crown-rump length; NICU: neonatal intensive care unit.

Table 4. Comparison of the incidence of neurodevelopmental disorders between twin pregnancies conceived through ART and those conceived spontaneously ^

	ART conception (n = 280)		Spontaneous conception (n = 178)		
	n	%	n	%	p
No	235	(89)	158	(84)	
Yes	45	(16)	20	(11)	<0.001
Language disorders	14	(5)	8	(4)	0.805
ASD	15	(5)	3	(4)	0.049
ADHD	0	(0)	2	(1)	0.075
PDD	0	(0)	1	(0.6)	0.209
Learning disorders	8	(3)	1	(0.6)	0.085
Behavioral disorders	4	(1.1)	2	(1.4)	0.780
Other	24	(1.7)	3	(1.0)	0.827

^ For those followed for 24 months or longer, this includes: language development disorders, ASD, ADHD, and PDD.
ASD: autism spectrum disorder; ADHD: attention-deficit/hyperactivity disorder; PDD: pervasive developmental disorder.

some risk to intrinsic maternal or paternal factors related to subfertility rather than to the treatments themselves.[30]

Observational studies have been published showing that specialized prenatal care programs for twin pregnancies were associated with better pregnancy outcomes, a lower incidence of preeclampsia, premature rupture of membranes, and delivery before 36 weeks, as well as a lower frequency of low birth weight and reduced neonatal morbidity.[31] Although clinical practice guidelines still show variability in monitoring protocols, this has decreased over time, and all agree that multiple pregnancies require special care.[32] Some studies have demonstrated a reduction in fetal mortality (primarily in

monochorionic pregnancies) following the implementation of the guidelines,[33] although studies on the impact of these recommendations are lacking.

The study's strengths include its protocol-based concurrent registry, comprehensive data collection from electronic medical records, and analysis adjusted for confounding variables. However, we must acknowledge its limitations, including its retrospective nature and its single-center design, which may limit the generalizability of the findings. Because this is a referral center, we cannot rule out selection bias; however, this bias would likely have worked against the null hypothesis of no difference, as it would have included women with a higher baseline burden of disease in the ART group.

Given the conflicting nature of the evidence, we believe our results are valid within the context of a tertiary care center with specialized follow-up in our country. However, they should be interpreted with caution, and it should be recognized that, at the population level, twin pregnancies resulting from ART may be associated with additional risks, particularly in the long term. In conclusion, in our cohort, twin pregnancies conceived through ART did not present a significant additional risk of maternal or perinatal complications when compared to those of spontaneous conception, despite differences in maternal baseline characteristics. These findings support the notion that, with appropriate perinatal management, the outcomes of twin pregnancies resulting from ART may be similar to those of natural conception. We recommend continuing to implement close monitoring programs for these pregnancies and conducting prospective multicenter studies with long-term follow-up to confirm these findings in different clinical settings. ■

The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2026/10997_AO_Izbizky_Anexo.pdf

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