How Have the Baseline Characteristics and Outcomes of Triplet Pregnancies Changed over the Last Two Decades?

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ABSTRACT

Objectives: Triplet pregnancies are high-risk pregnancies, and its baseline characteristics and gestational care protocols have changed over the years. The objective of this study is to compare the baseline characteristics and the prevalence of maternal, fetal, obstetric, and perinatal outcomes between triplet pregnancies conceived between 2013 and 2024 (period II [PII]) and those conceived between 2000 and 2012 (period I [PI]).

Methods: This was a single-centre, observational retrospective case−control study that included all triplet pregnancies followed up at the La Paz University Hospital between 2000 and 2024. Univariate and multivariate statistical studies were performed.

Results: A total of 234 triplet pregnancies were analyzed, with 140 in the PI group and 94 in the PII group. Maternal age ($P = 0.04$) and nulliparity rate ($P < 0.01$) were higher in the PII group, although pregnancies conceived through assisted reproductive techniques were more frequent in the PI group ($P = 0.04$). The percentage of dichorionic triamniotic pregnancies was significantly higher in the PII group ($P < 0.01$), and the percentage of trichorionic triamniotic pregnancies was significantly higher in the PI group ($P < 0.01$). Preeclampsia ($P < 0.01$), intrauterine growth restriction ($P < 0.01$), fetal death ($P < 0.01$), neonatal death ($P = 0.04$), and small for gestational age ($P < 0.01$) were significantly more frequent in the PII group. Threatened preterm labour ($P < 0.01$) and extremely premature births ($P < 0.01$) were significantly more frequent in the PI group. After adjusting for confounders, premature birth was the only outcome that remained significant (adjusted $P = 0.01$).

Conclusions: The baseline characteristics of the PII group (higher maternal age and higher rates of nulliparity and dichorionic triamniotic pregnancy) might be associated with a higher rate of obstetric and fetal complications during this period. Rates of premature birth and threatened preterm labour have decreased over the years, which is probably related to advances in gestational care.

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RÉSUMÉ

Objectif : Les grossesses triples sont des grossesses à risque élevé, et les caractéristiques de référence et les protocoles de soins de grossesse ont changé au fil des ans. L'objectif de cette étude est de comparer les caractéristiques de référence et la prévalence des issues maternelles, fœtales, obstétricales et périnatales dans les grossesses triples entre les périodes de 2013 à 2024 (PII) et de 2000 à 2012 (PI).

Méthodes : Il s'agit d'une étude cas-témoins observationnelle rétrospective monocentrique de toutes les grossesses triples suivies à l'hôpital universitaire de La Paz entre 2000 et 2024. Des analyses statistiques univariées et multivariées ont été réalisées.

Résultats : 234 grossesses triples ont été analysées : 140 dans le groupe PI et 94 dans le groupe PII. Dans le groupe PII, l'âge maternel était plus élevé ($P = 0{,}04$) et les femmes nullipares étaient plus nombreuses ($P < 0{,}01$), mais les grossesses conçues par technologies de procréation assistée étaient plus fréquentes dans le groupe PI ($P = 0{,}04$). Le pourcentage de grossesses bichoriales triamniotiques était significativement plus élevé ($P < 0{,}01$) dans le groupe PII, et le pourcentage de grossesses trichoriales triamniotiques était significativement plus élevé ($P < 0{,}01$) dans le groupe PI. La pré-éclampsie ($P < 0{,}01$), le retard de croissance intra-utérin ($P < 0{,}01$), la mort fœtale ($P < 0{,}01$), la mort néonatale ($P = 0{,}04$) et le petit poids pour l'âge gestationnel ($P < 0{,}01$) étaient significativement plus fréquents dans le groupe PII. La menace

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d'accouchement prématuré ($P < 0,01$) et la très grande prématurité ($P < 0,01$) étaient significativement plus fréquentes dans le groupe PI. Après ajustement pour tenir compte des facteurs de confusion, la prématurité est le seul facteur qui reste significatif ($P = 0,01$).

Conclusion : Les caractéristiques de référence du groupe PII (âge maternel plus élevé, prévalence plus élevée de femmes nullipares, et taux plus élevé de grossesses bichoriales triamniotiques) pourraient être associées à une élévation du taux de complications obstétricales et fœtales au cours de cette période. La fréquence de la prématurité et de la menace d'accouchement prématuré a diminué au fil des ans, probablement en raison des progrès réalisés en matière de soins de grossesse.

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INTRODUCTION

Triplet pregnancies have considerably increased over the past decades. This is mainly due to the rise in assisted reproductive techniques (ARTs).[1] Triplet pregnancies account for 0.15% of all pregnancies in our health care region.[2] Triplet pregnancies are considered high-risk pregnancies[3] and are associated with higher rates of maternal and fetal complications compared with singleton and twin pregnancies.[4,5] Many advances in pregnancy care have been made over the recent decades, with gestational control protocols and medication recommendations evolving over time.[6,7]

Only a few prior studies have compared maternal and neonatal outcomes in triplet pregnancies over the years.[8–10] Weissman et al.[9] did not find any differences in triplet pregnancy outcomes, while Skrablin et al.[8] and Kyeong et al.[10] concluded that reduced neonatal morbidity has been observed in the more recent period. We decided to analyze triplet pregnancies in our reference centre for the management of these pregnancies. We hypothesized that triplet pregnancy outcomes have improved in recent years compared with triplet pregnancies conceived in the recent past. Therefore, the objective of this study is to compare the baseline characteristics and the prevalence of maternal, fetal, obstetric, and perinatal outcomes between triplet pregnancies conceived in 2 periods of the 21st century in our centre.

MATERIALS AND METHODS

Study Design and Eligibility Criteria

This is a retrospective cohort study that compared triplet pregnancies conceived between 2000 and 2012 (period I [PI]) and triplet pregnancies conceived between 2013 and 2024 (period II [PII]). These groups were selected on the basis of the changes in triplet gestation care protocols established from 2011 to 2012 (Supplementary Material 1). Clinical information from medical records of triplet pregnancies followed at the Materno-Fetal Medicine Unit at La Paz University Hospital was retrieved after obtaining Research Ethics Committee approval (PI-5286 2022.168; date of approval: July 14, 2022). Informed consent was not required in this observational retrospective study. The diagnosis of triplet pregnancies and the determination of amnionicity, chorionicity, and gestational age were made by expert sonographic obstetricians in the first trimester at our centre. Chorionicity was confirmed after birth by pathological examination of the placenta. Inclusion criteria encompassed patients with triplet pregnancies from the onset, diagnosed either at our centre or at other centres with subsequent confirmation at our centre, who were monitored and who delivered at our hospital. Exclusion criteria encompassed women who did not deliver in our hospital, those lost to follow-up during pregnancy, and those who initially had a triplet pregnancy but opted for selective reduction of to a twin or singleton pregnancy.

Study Variables

The collected data were maternal age, maternal pre-pregnancy maternal body mass index (BMI), pre-existing medical conditions associated with infertility, parity, year of conception, conception type, maternal complications, fetal complications, perinatal outcomes, threatened preterm labour (TPL) (labour <32 weeks), premature rupture of membranes (PROM), preventive cervical cerclage (in the first trimester), cesarean delivery type, and preterm birth (extremely preterm [<28 weeks], very preterm [28–31.7 weeks], and moderate to late preterm [32–37 weeks]).

Statistical Analysis

Quantitative variables were expressed as means and standard deviations for normally distributed variables, or medians and interquartile ranges for non-normally distributed variables. Qualitative variables were expressed as frequencies and percentages. The Kolmogorov-Smirnov (K-S) test was used to determine if quantitative variables were normally distributed. Qualitative variables were analyzed using the χ^2 or Fisher exact test, while parametric quantitative variables were analyzed using the t test, and non-parametric quantitative variables using the Mann-Whitney U test. The selected association measure for qualitative variables was the odds ratio (OR) with a 95% confidence interval (CI). To identify factors associated with complications (confounders), a logistic regression model was constructed, with PI versus PII as the dependent variable and potential prognostic factors as

independent variables. These variables were selected on the basis of significant differences observed in the initial analysis (maternal age, parity, preeclampsia, dichorionic triamniotic [DCTA], monochorionic triamniotic [MCTA], conception mode, intrauterine growth restriction, biometry discordance, fetal death, neonatal death, birth weight, umbilical cord pH, threatened preterm labour, gestational delivery age, preterm birth <28 weeks, and non-premature births). All performed tests were 2-tailed, and a statistically significant difference was considered when the *P* value was ≤0.05. Statistical analysis of the data was performed using the IBM SPSS Statistics software, Version 25.0 (IBM Corp., Armonk, NY).

RESULTS

At the beginning of the study, all triplet pregnancies followed between 2000 and 2024 were recruited (263 pregnant women). A total of 24 pregnant woman (9.1%) opted for selective reduction of triplets to a twin or singleton pregnancy. From the 239 pregnant women who decided to continue with a triplet pregnancy, 5 were lost to follow-up (1 was lost during pregnancy and 4 did not deliver in our hospital). Finally, 234 patients were analyzed in this study, with 140 in the PI group and 94 in the PII group (Figure). The results are summarized in Tables 1 to 3.

Regarding the mode of conception, 74.4% of pregnancies were conceived by artificial insemination, in vitro fertilization, or intracytoplasmic sperm injection. Differences were statistically significant ($P = 0.04$; OR = 0.53 [0.29−0.96]). Two embryos were transferred in 121 cases (69%) (82 in PI vs. 39 in PII), and 3 embryos were transferred in 21 cases (12%) (13 in PI vs. 8 in PII). The most frequent subfertility causes were polycystic ovary syndrome and endometriosis.

From our triplet pregnancies, 66.7% were trichorionic triamniotic (TCTA), 26.9% were DCTA, and 6.4% were MCTA. Differences between DCTA and TCTA pregnancies were statistically significant ($P < 0.01$; OR = 5.60 [2.98−10.53] and OR = 0.16 [0.09−0.31], respectively). Maternal age did not follow a normal distribution (K-S test, $P = 0.02$). The overall median age was 35 years (25th percentile [P25] = 32; 75th percentile [P75] = 37). Statistically significant differences were observed between the groups ($P = 0.04$). Pre-pregnancy maternal BMI did not follow a normal distribution (K-S test, $P < 0.01$). The overall median BMI was 24.1 kg/m^2 (P25 = 22.6; P75 = 25.6). No statistically significant differences were observed between the groups ($P = 0.90$). Regarding maternal parity, 52.6% were nulliparous women. The difference between the groups was statistically significant ($P < 0.01$; OR = 0.43 [0.25−0.73]). Regarding maternal complications, there was a significantly higher incidence of preeclampsia in the PII group ($P < 0.01$; OR = 5.45 [1.72−17.30]).

Figure. Inclusion and exclusion criteria. Number of pregnant women and fetuses included.

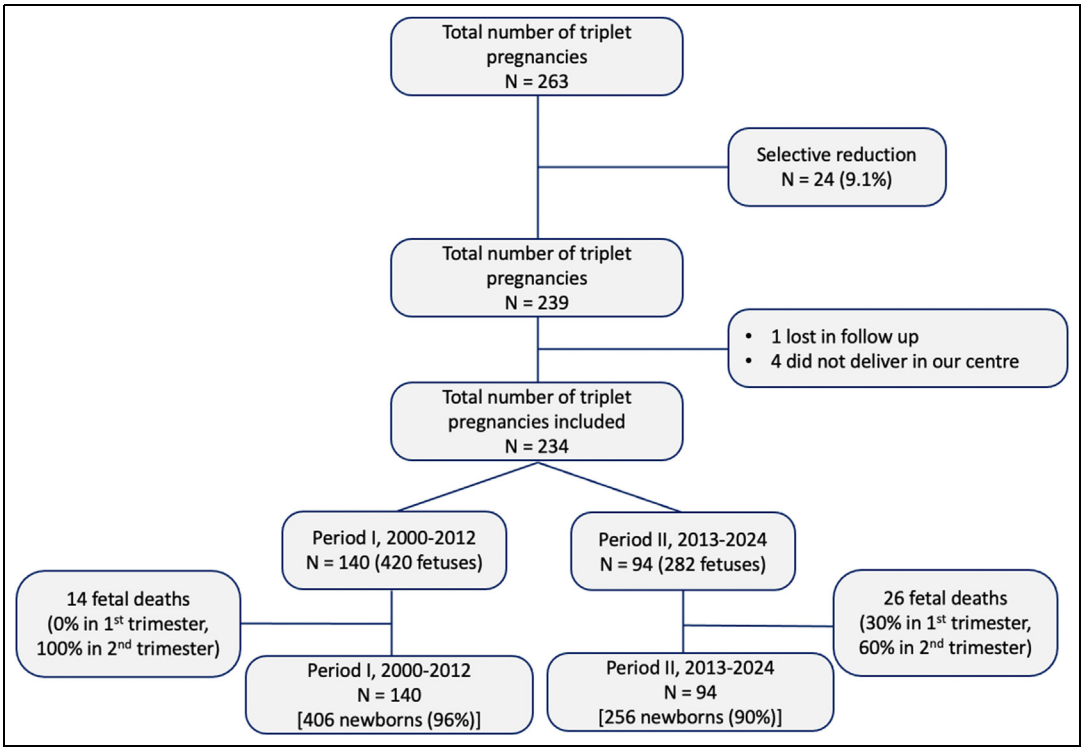

Table 1. Description of maternal characteristics and maternal complications

Variable	Total, n = 234	Period I (2000–2010), n = 140	Period II (2011–2021), n = 94	Significance (*P*)	Odds ratio	95% CI	Significance (*P*) after adjustment	OR after adjustment	95% CI after adjustment
Maternal characteristics									
Maternal age (y)	35 (P25 = 32, P75 = 37)	34 (P25 = 32, P75 = 36,75)	35 (P25 = 33, P75 = 38)	0.04[a]	-	-	0.05	1.36	0.99–1.85
Pre-pregnancy BMI (kg/m^2)	24.1 (P25 = 22.6, P75 = 25.6)	24.0 (P25 = 22.57, P75 = 25.60)	24.5 (P25 = 22.67, P75 = 25.62)						
- <30	169 (96.0)	100 (94.3)	69 (98.6)	0.90	0.24	0.02–2.05			
- ≥30	7 (4.0)	6 (5.7)	1 (1.4)	0.16					
Parity									
- Nulliparous women	123 (52.6)	62 (44.3)	61 (64.9)	<0.01[a]	0.43	0.25–0.73	0.65	0.74	0.34–2.45
- Multiparous women	111 (47.4)	78 (55.7)	33 (35.1)						
Maternal complications									
Preeclampsia	17 (7.3)	4 (2.9)	13 (13.8)	<0.01	5.45	1.72–17.30	0.96	0.92	0.02–31.02
Gestational hypertension	7 (3.0)	4 (2.9)	3 (3.2)	1.00	1.12	0.24–5.12			
Gestational diabetes	16 (6.9)	7 (5.0)	9 (9.6)	0.19	2.01	0.72– 5.60			
Intrahepatic cholestasis	17 (7.3)	11 (7.9)	6 (6.4)	0.80	0.80	0.28– 2.24			
Pregnancy-induced hypothyroidism	19 (8.2)	11 (7.9)	8 (8.6)	1.00	1.10	0.42–2.85			
Iron deficiency anaemia	43 (18.4)	30 (21.4)	13 (13.8)	0.16	0.58	0.28–1.19			

[a]Statistically significant differences.

P25: 25th percentile; P75: 75th percentile.

Table 2. Description of chorionicity, fetal complications, and neonatal complications

Variable	Total, n = 234	Period I (2000–2010), n = 140	Period II (2011–2021), n = 94	Significance (*P*)	Odds ratio	95% CI	Significance (*P*) after adjustment	OR after adjustment	95% CI after adjustment
Chorionicity									
- MCTA	15 (6.4)	6 (4.3)	9 (9.6)	0.17	2.36	0.81–6.88			
- DCTA	63 (26.9)	19 (13.6)	44 (46.8)	<0.01[a]	5.60	2.98–10.53	0.54	3.06	0.08–112.70
- TCTA	156 (66.7)	115 (82.1)	41 (43.6)	<0.01[a]	0.16	0.09–0.31	0.19	0.12	0.06–2.86
Conception mode									
- Spontaneous	60 (25.6)	29 (20.7)	31 (33.0)	0.04[a]	0.53	0.29–0.96	0.99	-	-
- AI, FIV, ICSI	174 (74.4)	111 (79.3)	63 (67.0)						
Fetal complications									
Intrauterine growth restriction	19 (8.1)	6 (4.3)	13 (13.8)	0.01[a]	3.58	1.31–9.80	0.25	0.05	0.01–7.71
Twin-to-twin transfusion syndrome	5 (2.1)	1 (0.7)	4 (4.3)	0.16	6.17	0.68–56.16			
Twin anaemia-polycythemia sequence	1 (0.4)	0 (0)	1 (1.1)	0.40	0.39	0.34–0.46			
Amniotic fluid discordance	12 (5.1)	4 (2.9)	8 (8.5)	0.07	3.16	0.92–10.82			
Biometry discordance (>25%)	11 (4.7)	1 (0.7)	10 (10.6)	<0.01[a]	16.54	2.08–131.58	0.40	7.77	0.63–42.10

Variable	Total, n = 702	Period I (2000–2010), n = 420	Period II (2011–2021), n = 282	Significance (*P*)	Odds ratio	95% CI	Significance (*P*) after adjustment	OR after adjustment	95% CI after adjustment
Fetal complications									
Fetal malformations	7 (1.0)	2 (0.5)	5 (1.8)	0.12	3.77	0.72–19.58			
Fetal death	40 (5.7)	14 (3.3)	26 (9.2)	<0.01[a]	2.94	1.51–5.74	0.19	15.64	0.25–52.63

Variable	Total, n = 662	Period I (2000–2010), n = 395	Period II (2011–2021), n = 267	Significance (*P*)	Odds ratio	95% CI	Significance (*P*) after adjustment	OR after adjustment	95% CI after adjustment
Neonatal complications									
Neonatal death	6 (0.9)	1 (0.3)	5 (1.9)	0.04[a]	7.51	0.87–64.72	0.99	-	-
Birth weight (g)	1828 ± 407	1907 ± 404	1757 ± 397	<0.01[a]	-	-			
- <1500	95 (19.8)	40 (17.9)	55 (21.5)	0.62	1.11	0.71–1.75	0.99	-	-
- 1500–2500	360 (75.0)	167 (74.6)	193 (75.4)	0.43	1.17	0.78–1.75			
- >2500	25 (5.2)	17 (7.6)	8 (3.1)	0.02[a]	0.44	0.20–0.93			

(continued)

Table 2. *(Continued)*

Variable	Total, n = 234	Period I (2000 −2010), n = 140	Period II (2011 −2021), n = 94	Significance (*P*)	Odds ratio	95% CI	Significance (*P*) after adjustment	OR after adjustment	95% CI after adjustment
Umbilical cord pH	7.31 (P25 = 7.28, P75 = 7.34)	7.30 (P25 = 7.26, P75 = 7.33)	7.33 (P25 = 7.30, P75 = 7.35)						
- <7.20	34 (6.1)	10 (4.0)	24 (7.8)	<0.01[a]	0.48	0.22−1.02	0.99	-	-
- ≥7.20	525 (93.9)	243 (96.0)	282 (92.2)	0.07					
Apgar score at 5 min									
- ≤5	33 (6.6)	19 (7.6)	14 (5.5)	0.37	0.72	0.34−1.45			
- >5	470 (93.4)	231 (92.4)	239 (90.2)						

[a]Statistically significant differences.

AI: artificial insemination; DCTA: dichorionic triamniotic; FIV: fertilisation in vitro; ICSI: intracytoplasmic sperm injection; MCTA: monochorionic triamniotic; P25: 25th percentile; P75: 75th percentile; TCTA: trichorionic triamniotic.

There were no differences in the other maternal complications between the groups.

Regarding fetal complications, 19 patients (8.1%) had a fetus with fetal growth restriction (FGR) ($P = 0.01$; OR = 3.58 [1.31−9.80]). There were no significant differences in any of the other fetal complications between the groups.

Among the 702 fetuses, malformations appeared in 7 cases (aberrant right subclavian artery [4 cases], pentalogy of Cantrell, Down syndrome, and tetralogy of Fallot). No significant differences were observed between the groups. Fetal death was observed in 40 fetuses (5.7%). The difference between the groups in fetal death rates was statistically significant ($P < 0.01$; OR 2.94 [1.51−5.74]). Miscarriages and fetal death occurred between weeks 9 and 27, with 20% in the first trimester and 80% in the second trimester. No fetal death occurred during the third trimester. Selective occlusion of the umbilical cord due to malformations or severe FGR occurred in 18 patients (1 MCTA, 11 DCTA, 7 TCTA; 7 in PI group and 11 in PII group), and spontaneous loss of all 3 fetuses occurred in 5 patients (1 in PI group and 4 in PII group) (Figure).

Preventive cervical cerclage in the first trimester was used in 21.8% of the cases, with no statistically significant difference between the groups. Regarding obstetric complications, 53 cases (22.6%) presented with PROM, with no statistically significant differences between the groups. TPL occurred in 104 cases (44.4%), with a statistically significant difference between the groups ($P < 0.01$; OR 0.35 [0.20−0.62]).

In all 229 cases, a cesarean delivery was performed. Statistically significant differences were observed between the groups for all cesarean delivery types. Gestational delivery age did not follow a normal distribution ($P < 0.01$). Differences between the groups were statistically significant ($P = 0.02$), with a median gestational delivery age of 33 weeks (P25 = 31; P75 = 35). After group stratification, differences were observed in extremely preterm births ($P < 0.01$; OR 0.19 [0.05−0.67]), moderate to late preterm births ($P < 0.01$; OR 4.24 [2.15−8.35]), and non-preterm births ($P = 0.01$; OR 0.59 [0.52−0.66]) groups.

Among the 662 newborns, differences in neonatal mortality were observed ($P = 0.04$; OR 7.51 [0.87−64.72]). Birth weight followed a normal distribution ($P = 0.09$). Mean birth weight was 1828 ± 407 g.

Table 3. Description of obstetric complications, cesarean delivery, and premature births

Variable	Total, n = 234	Period I (2000–2010), n = 140	Period II (2011–2021), n = 94	Significance (*P*)	Odds ratio	95% CI	Significance (*P*) after adjustment	OR after adjustment	95% CI after adjustment
Obstetric complications									
Premature rupture of membranes	53 (22.6)	37 (26.4)	16 (17.0)	0.11	0.57	0.29–1.10			
Threatened preterm labour	104 (44.4)	76 (54.3)	28 (29.8)	<0.01[a]	0.35	0.20–0.62	0.11	0.14	0.01–1.57
Preventive cervical cerclage	51 (21.8)	27 (19.3)	24 (25.5)	0.26	1.43	0.76–2.68			
Variable	Total, n = 229	Period I (2000–2010), n = 139	Period II (2011–2022), n = 90	Significance (*P*)	Odds ratio	95% CI	Significance (*P*) after adjustment	OR after adjustment	95% CI after adjustment
Cesarean delivery type									
- Scheduled	109 (47.6)	87 (62.6)	22 (24.4)	<0.01[a]	0.19	0.10–0.34			
- Maternal pathology	17 (7.4)	15 (10.8)	2 (2.2)	0.02[a]	0.18	0.04–0.84			
- Fetal well-being loss risk	29 (12.7)	25 (18.0)	4 (4.4)	<0.01[a]	0.21	0.07–0.63			
- PROM	47 (20.5)	12 (8.6)	35 (38.9)	<0.01[a]	6.73	3.25–13.94			
- Labour	27 (11.8)	0 (0)	27 (30.0)	<0.01[a]	0.31	0.25–0.38			
Gestational delivery age, wk	33 (P25 = 31, P75 = 35)	33 (P25 = 30, P75 = 34)	34 (P25 = 32, P75 = 35)	0.02[a]	-	-	0.03[a]	0.67	0.46–0.97
- <28	24 (10.5)	21 (15.1)	3 (3.3)	<0.01[a]	0.19	0.05–0.67	0.01[a]	0.46	0.28–0.68
- 28–31.7	38 (16.6)	28 (20.1)	10 (11.1)	0.07	0.49	0.22–1.07			
- 32–37	158 (69.0)	81 (58.3)	77 (85.6)	<0.01[a]	4.24	2.15–8.35	0.06		
- >37	9 (3.9)	9 (6.5)	0 (0)	0.01[a]	0.59	0.52–0.66	0.02[a]	0.56	0.35–0.76

[a]Statistically significant differences.

P25: 25th percentile; P75: 75th percentile; PROM: premature rupture of membranes.

Differences between the groups were observed ($P < 0.01$). After group stratification, differences were observed only in the >2,500 g group ($P = 0.02$; OR 0.44 [0.20−0.93]).

Umbilical cord pH did not follow a normal distribution (K-S test $P < 0.01$). Umbilical cord mean pH was 7.31 (P25 = 7.28; P75 = 7.34). Differences were observed between the groups ($P < 0.01$). Apgar test score at 5 minutes was ≤5 in 34 cases (6.6%), with no statistically significant difference between the groups.

Logistic regression multivariate analysis (Cox R square 27.1%) including variables with statistically significant P values showed adjusted $P = 0.03$ and adjusted OR 0.67 (0.46−0.97) for preterm births, adjusted $P = 0.01$ and adjusted OR 0.46 (0.28−0.68) for extremely preterm births, and adjusted $P = 0.02$ and adjusted OR 0.56 (0.35−0.76) for non-preterm births.

DISCUSSION

Principal Findings

Our study suggests that more recent triplet pregnancies are associated with lower rates of preterm birth but slightly worse maternal, fetal, and obstetric outcomes compared with those in the past.

General Results

In our study, 234 pregnant women and 702 fetuses were analyzed, representing the largest reported cohort in triplet studies to the best of our knowledge.[8−10] This study provides a contemporary analysis of triplet pregnancies in the 21st century. To our knowledge, this is the largest and most up-to-date study analyzing triplet gestations.

Subfertility and ART Results

A total of 79.3% of our triplet pregnancies were conceived using ART in the PI group and 67% in the PII group, as was the case in the study by Kyeong et al.[10] In the studies by Weissman et al.[9] and Skrablin et al.,[8] the percentage of ART triplet pregnancies is not mentioned. The decrease in triplet pregnancies conceived via ART over the years is due to the tendency to transfer only 1 embryo in fertility clinics. In general, ART pregnancies have been associated with poorer obstetric outcomes.[11] Only a few prior studies have compared maternal and neonatal outcomes between spontaneous and ART triplet pregnancies. Some of these studies found no differences between groups,[11,12] and 1 study suggested high levels of neonatal morbidity in the ART group.[13] The most common causes of subfertility in our pregnant mothers were the same as those found by Fennessy et al.[11]: polycystic ovary syndrome and endometriosis.

Chorionicity Results

MCTA and DCTA pregnancy outcomes are worse than those of TCTA pregnancies,[3,14−16] especially those related to twin-to-twin transfusion syndrome (TTTS) or twin anaemia-polycythemia sequence (TAPS).[17] TCTA pregnancies have a lower risk of death and preterm birth and have higher birth weights.[15] This type of pregnancy was the most prevalent chorionicity type in our series, consistent with previous reports.[10−12] In our study, TCTA pregnancies were more prevalent in the PI group, while DCTA and MCTA pregnancies were more prevalent in the PII group. This could be explained by the increasing tendency to transfer only 1 or 2 embryos at the blastocyst stage over the years. The statistically significant difference between groups in the chorionicity percentage disappeared after adjusting for confounders, although it may have contributed to the higher rate of maternal and fetal complications in the PII group. In this group, most patients were nulliparous, which is concordant with previous studies.[9,10]

Maternal Outcomes

Regarding maternal characteristics, the maternal age was higher in the PII group, as in previous studies.[8−10] Although this statistically significant difference disappeared upon adjusting for confounders, it could have contributed to the higher percentage of complications in the PII group. No differences were found in pre-pregnancy maternal BMI between our groups. Similar information was not reported in other series.[8−10] In our series, preeclampsia was the only maternal complication that showed statistically significant differences between the groups; however, these differences were no longer significant after adjusting for confounders. This may have contributed to worse fetal outcomes in the PII group. Risk factors related to preeclampsia in the PII group included higher maternal age, a greater number of nulliparous women, and increased use of oocyte donation. All patients with triplet pregnancies had been receiving preventive aspirin treatment in our hospital over the last years to decrease the risk of preeclampsia. The most frequent maternal complication in our cases was anemia, which is concordant with the study by Kyeong et al.[10] Anemia was more frequent in the PI group, likely because over the recent years, all triplet pregnancies have been supplemented with iron from the first trimester. Kyeong et al.[10] found a decreased incidence of both preeclampsia and anaemia in the more recent group, but these authors had established a protocol for triplet pregnancy management

and control in their PII group that might be related to that decrease.

Fetal Outcomes

After adjusting for confounders, the statistically significant difference in FGR disappeared. The higher rate of this complication in the PII group might be related to the higher percentage of MCTA and DCTA pregnancies. We found no differences in the other fetal complications individually, as in previous studies.[8–10] Kyeong et al.[10] (2019) concluded that the composite morbidity in the more recent period significantly decreased. No previous articles have compared the malformation rates, and our study found no differences. We found statistically significant differences in fetal deaths, but these differences disappeared after adjusting for confounders. This may be related to higher rates of DCTA and MCTA pregnancies, which are associated with increased incidence of TTTS, TAPS, and intrauterine growth restriction.

Obstetric Outcomes

Regarding obstetric outcomes, other authors found that TPL was one of the most common complications,[8] as was the case in our series, in which TPL occurred in 44.4% of the triplet pregnancies. The PII group had lower rates of TPL, likely because midwives and obstetricians now advise all women expecting triplets to reduce physical activity. After adjusting for confounders, the statistically significant difference in TPL rates disappeared. No other studies have found differences in TPL rates between groups.[8–10]

Preventive cervical cerclage was used in 21.8% of the cases, which is a higher rate than the 9% reported by Kyeong et al.[10] and lower than the 65% reported by Skrablin et al.[8] In our study, there was no significant increase in preventive cerclage in the PII group. This technique did not reduce preterm birth rates and is now only used in selected triplet pregnancies with previous poor obstetric outcomes. PROM occurred in 22.6% of our cases, which is a higher rate compared with 14.1% of the cases in the study by Skrablin et al.[8] and a lower rate compared with 27.3% of the cases in the study by Kyeong et al.[10] PROM decreased in the PII group, likely because of the recommendation to reduce physical activity and take sick leave, although this decrease was not statistically significant.

Cesarean Delivery Results

Cesarean delivery was performed in all our cases, as in a previous study.[9] In the study by Kyeong et al., the cesarean deliveries were performed in 95.4% of the cases.[10] In our series, scheduled cesarean deliveries were more frequent than those performed for maternal indications or fetal complications in both periods. This is due to the close monitoring of triple pregnancies at our hospital.

Preterm Birth Results

In our series, the large majority of gestations reached the expected duration for triplet pregnancies (34−35 weeks). All deliveries occurring after week 37 were within the PI group, due to old protocols. Mean gestational delivery time was 33 weeks, and there were more preterm births in the PI group. We found differences that remained statistically significant after adjusting for confounders, which were not consistent with other published series.[8–10] In the PII group, there were fewer cases of extremely premature and very premature newborns because of changes in triplet pregnancy care protocols (monthly cervicometry from week 20, cervical pessary placement and progesterone administration in short cervix cases, maintenance tocolysis with intravenous atosiban in cases of uterine contractions, recommendation to reduce physical activity, etc.). Nevertheless, Kyeong et al.[10] and Weissman et al.[9] did not find a decrease in extremely premature newborns over the years.

Neonatal Outcomes

Mean birth weight was 1828 ± 407 g, and we found differences between groups that persisted after stratification but disappeared after adjusting for confounders. Other studies did not report significant differences.[8–10] The higher birth weight (>2500 g) observed in the PI group might be related to more favourable baseline characteristics and lower complication rates in this period. We found no statistically significant differences in the Apgar test results at 5 minutes, consistent with Skrablin et al.[8] We found statistically significant differences in neonatal deaths, but these differences disappeared after adjusting for confounders. The higher rate in the PII group could be explained by the higher rates of maternal and fetal complications in this group.

Clinical and Research Implications

More recent triplet pregnancies were associated with higher maternal age, a greater proportion of nulliparous women, higher rates of DCTA, and increased use of oocyte donation. Tailoring pregnancy management to address complications related to these factors may help maintain similar outcomes despite these baseline characteristics.

Strengths and Limitations

Some of the strengths of our study include the exhaustive data collection from a very large cohort and the use of both univariate and multivariate analyses. Kyeong et al.[10] applied multivariate analysis in their study, whereas

Table 4. Previous published studies and their findings compared with this study's findings

Study	Skrablin et al.	Weissman et al.	Kyeong et al.	Pena-Burgos et al. (present study)
Year	2002	2013	2019	2024
Number of triplets included	85	63	65	234
	44 in the PI group (1986–1995) vs. 41 in the PII group (1986–2000)	29 in the PI group (1978–1987) vs. 34 in the PII group (2001–2011)	22 in the PI group (1992–2001) vs. 43 in the PII group (2003–2013)	140 in the PI group (2000–2010) vs. 94 in the PII group (2011–2021)
Study type	Retrospective unicentric cohort study	Retrospective unicentric cohort study	Retrospective bicentric study	Retrospective unicentric cohort study
Statistical analysis	Univariate	Univariate	Univariate and multivariate	Univariate and multivariate
Most frequent subfertility causes	Not mentioned	Not mentioned	Not mentioned	Polycystic ovary syndrome and endometriosis
Most frequent chorionicity type	Not mentioned	Not mentioned	TCTA	TCTA
Maternal age	No differences	No differences	No differences	No differences
	PI (31.0 ± 4.1) vs. PII (32.3 ± 3.8)	PI (26.9 [22–37]) vs. PII (30.7 ± 5 [19–41])	PI (31.4 ± 4.2) vs. PII (31.9 ± 4.0)	PI (34 [P25 = 32, P75 = 36,75]) vs. PII (35 [P25 = 33, P75 = 38])
Maternal BMI	Not studied	Not studied	Not studied	No differences
				PI (24.0 [P25 = 22.57, P75 = 25.60]) vs. PII (24.5 [P25 = 22.67, P75 = 25.62])
Maternal complications	Preeclampsia (0%); anemia (PI [68.2%] vs. PII [30.2%]); gestational diabetes (PI [0%] vs. PII [2.4%]); intrahepatic cholestasis (PI [2.3%] vs. PII [0%])	Not studied	More preeclampsia and anemia in PI group	No differences
			Preeclampsia (PI [31.8%] vs. PII [2.3%]); anemia (PI [68.2%] vs. PII [30.2%]); gestational diabetes (PI [0%] vs. PII [4.7%])	Preeclampsia (PI [2.9%] vs. PII [13.8%]); iron deficiency anemia (PI [21.4%] vs. PII [13.8%]); gestational hypertension (PI [2.9%] vs. PII [3.2%]); gestational diabetes (PI [2.9] vs. PII [3.2]); intrahepatic cholestasis (PI [7.9%] vs. PII [6.4%]); pregnancy-induced hypothyroidism (PI [7.9%] vs. PII [8.6%])
Most frequent maternal complication	Not mentioned	Not mentioned	Anemia	Anemia
Parity	Not studied	Not studied	No differences	No differences
			Nulliparity (PI [77.3%] vs. PII [79.1%])	Nulliparity (PI [44.3%] vs. PII [64.9%])
Fetal complications	No differences	No differences	Composite morbidity decreased in PII group	No differences

(continued)

Table 4. *(Continued)*

Study	Skrablin et al.	Weissman et al.	Kyeong et al.	Pena-Burgos et al. (present study)
	IUGR (PI [50.8%] vs. PII [43.3%])	Newborn hospitalization (PI [25 ± 21 (1−113)] vs. PII [31.4 ± 23.1 (6−134)])	(PI [26.2%] vs. PII [8.1%])	IUGR (PI [4.3%] vs. PII [13.8%]); TTTS (PI [0.7%] vs. PII [4.3%]); TAPS (PI [0%] vs. PII [1.1%]); amniotic fluid discordance (PI [2.9%] vs. PII [8.5%]); biometry discordance >25% (PI [0.7%] vs. PII [10.6%])
Obstetric outcomes	More PROM in PII group	Not studied	No differences	No differences
	Premature rupture of membranes (PI [4.5%] vs. PII [24.4%]), threatened preterm labour (PI [86.3%] vs. PII [82.9%])		Premature rupture of membranes (PI [27.3%] vs. PII [14.0%]), threatened preterm labour (PI [31.8%] vs. PII [44.2%])	Premature rupture of membranes (PI [26.4%] vs. PII [17.0%]), threatened preterm labour (PI [54.3%] vs. PII [29.8%])
Malformations	Not studied	Not studied	Not studied	No differences
				(PI [0.5%] vs. PII [1.8%])
Cesarean delivery 100% cases	No	Yes	No	Yes
Mean gestational delivery age	No differences	No differences	More extremely preterm birth and more non- preterm birth in PII group	More extremely preterm birth and more non-preterm birth in PI group
	PI (33.1 ± 3.9) vs. PII (32.6 ± 4.2)	<28 wk (PI [3%] vs. PII [6%]); >34 wk (PI [19.7%] vs. PII [42.7%])	<28 wk (PI [0%] vs. PII [9.7%]); >34 wk (PI [19.7%] vs. PII [42.7%])	<28 wk (PI [15.1%] vs. PII [3.3%]); 28−31.7 wk (PI [20.1%] vs. PII [11.1%]); 32−37 wk (PI [58.3%] vs. PII [85.6%]); >37 wk (PI [6.5%] vs. PII [0%])
	Less <28 wk in PII group			
Neonatal death	Decreases in perinatal mortality	No differences	No differences	No differences
	PI (235%) vs. PII (142%)	PI (13.8%) vs. PII (6.9%)	PI (0%) vs. PII (0.8%)	PI (0.3%) vs. PII (1.9%)
Mean birth weight	No differences	No differences	No differences	No differences
	PI (1562 ± 601) vs. PII (1494 ± 560)	PI (1713 ± 472) vs. PII (1673 ± 465)	PI (1574 ± 407) vs. PII (1683 ± 440)	PI (1907 ± 404) vs. PII (1757 ± 397)
Other neonatal complications	No differences	No differences	No differences	No differences
	Apgar score at 5 min (PI [9 (2−10)] vs. PII [9 (1−10)])	Apgar score at 5 min (8 ± 1 in both groups)	Apgar score <7 at 5 min (PI [23.0%] vs. PII [5.6%])	pH <7.20 (PI [4.0%] vs. PII [7.8%]); Apgar score ≤5 at 5 min (PI [7.6%] vs. PII [5.5%])

IUGR: intrauterine growth restriction; P25: 25th percentile; P75: 75th percentile; PI: period I; PII: period II; PROM: premature rupture of membranes; TAPS: twin anemia-polycythemia sequence; TCTA: trichorionic triamniotic; TTTS: twin-to-twin transfusion syndrome.

Weissman et al.[9] did not adjust for confounders. The small sample sizes in those studies may have limited their statistical power. One of the main limitations of our study was its retrospective design, which is subject to inherent biases. Some data were unavailable in the medical reports, mainly the infertility cause and neonatal information. We were unable to collect some relevant information on maternal characteristics that could influence the results, such as economic status or tobacco and alcohol consumption. The only pre-existing maternal disorders included were those related to infertility. Another major source of bias in our study was that all ART types were analyzed together, despite some past studies concluding that there are differences in complications between oocyte donors and non-oocyte donors.[18,19] Including patients with selective reductions could skew our results given that fetal complications are a part of our outcomes. In addition, another limitation of our study was the lack of inclusion of long-term neonatal outcomes.

The findings of previous published studies compared with those of the present study are summarized in Table 4.

CONCLUSIONS

In conclusion, the demographic profile of women with triplet pregnancies has changed over the years, with higher maternal age, a greater proportion of nulliparous women, and increased use of oocyte donation in ART. This may explain the higher rates of preeclampsia but not gestational diabetes in recent years. Over the last decade, there has been an increased prevalence of MCTA and DCTA placentas due to the transfer of 1 or 2 blastocysts, which may be related to the higher rates of fetal complications such as FGR, low birth weight, fetal death, TTTS, TAPS, and neonatal death. Nevertheless, because of the new gestational care protocols, the rates of preterm birth (<32 weeks) have decreased in recent years.

AUTHOR CONTRIBUTIONS

- Conception and design of the study and acquisition and analysis of data: Pena-Burgos EM, Duyos-Mateo I, De La Calle M.
- Statistical design and analysis: Quirós-González V.
- Drafting the manuscript: Pena-Burgos EM, Duyos-Mateo I, Pozo-Kreilinger JJ, Regojo-Zapata RM, Quirós-González V, De La Calle M.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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