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Maternal and Perinatal Outcomes in Spontaneous Twins versus Twins Conceived By Ovulation Induction and Assisted Reproductive Techniques: A Cross-Section Study

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ABSTRACT

Twin pregnancies have a higher perinatal mortality and morbidity and increased obstetrical complications compared with singleton pregnancies, and assisted reproduction techniques (ART) have increased twin pregnancy rates. This study was performed to compare perinatal and obstetric outcomes of dichorionic twin pregnancy following ART with those from spontaneous pregnancy. This cross-sectional study was performed in the Erbil Maternity Teaching Hospital. Two-hundred dichorionic twin pregnancies were classified into two groups: spontaneous (n = 121) and ART (n = 79) groups. Basic criteria included demographic data, gestational age, mode of delivery, pregnancy complications (preeclampsia, gestational diabetes, preterm labor, anemia, blood transfusion, postpartum hemorrhage), neonatal outcomes (weight, first and fifth minute Apgar score, neonatal intensive care unit admission, respiratory distress, and sepsis). The rates of pregnancy induced by hypertension, gestational diabetes, and pre-labor preterm rupture of membrane were significantly higher in the ART group, but postpartum hemorrhage, blood transfusion, anemia, were not significantly different. The majority of women in the ART group delivered by caesarean section. The risks of preterm birth, low neonatal birth weight and congenital malformation, and moderately depressed Apgar scores were higher in the ART group, while no significant differences were detected regarding other outcomes. In our study, the second twin had a worse outcome compared with the first twin in both groups of conception. Maternal and neonatal outcomes were poorer in the ART group. The second twin had a worse outcome compared with the first twin in both groups.

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Introduction

Assisted reproductive technology (ART) has become a widespread choice for the treatment of human infertility during recent decades, and one consequence has been the progressive rise in the incidence of twin pregnancies [1, 2]. Twin pregnancies are associated with an increased risk of maternal morbidity and mortality, and an increased incidence of neonatal morbidity and mortality compared with singleton pregnancies [3-5]. Variable results have been reported for neonatal and maternal outcomes, and the findings may depend on differences in the studied populations and/or in the management approach of twin pregnancy. There are conflicting data of pregnancy outcomes of twins conceived by ART compared with those naturally conceived (NC).

A systematic review in 2004 and a large study in 2008 both suggested that in cases of twin pregnancy after assisted conception, the perinatal mortality was significantly lower compared with those spontaneously conceived [3,4,6]. Another review found an increase in antenatal complications for assisted-conception twin pregnancies, but only limited effects on the morbidity and mortality of an individual pregnancy [6]. In contrast, a recent 2015 study showed an increased risk of adverse neonatal outcomes,

including stillbirth, low gestational weight, preterm birth, sepsis and low Apgar scores, in twins conceived by ART compared with spontaneously conceived twins. In addition, ART twins have an increased rate of cesarean delivery, especially twins from in vitro fertilization, although there were no significant differences in the incidences of perinatal death or congenital malformations [6-8].

The current study was conducted in a very busy maternity hospital, which is the only public hospital in the city, to compare both maternal and perinatal outcomes in twin pregnancies spontaneously conceived or conceived by successful ART. To get the most observations

Materials and Methods

Study design and location

This is a cross-sectional study of 200 twins performed in the Maternity Teaching Hospital, Erbil city, Kurdistan region/Iraq, from 1 November 2016 to 31 December 2017.

Inclusion and Exclusion Criteria

Twins meeting the inclusion criteria were enrolled from 1 November 2016 to 1 December 2017. The criteria for inclusion

included diachronic diamniotic twins delivered >24-week gestational age with individual weights ≥ 500 g [9]. Exclusion criteria included intrauterine fetal deaths, higher-order multiple pregnancies, singleton pregnancy deliveries complicated by early vanishing fetuses, twin pregnancies reduced to singleton, and triple pregnancy reduced to twin.

Data Collection

In this study, twins were identified in the outpatient clinic and labor ward and classified into two groups, iatrogenic conceived twins (ART or medical ovulation induced mainly by clomiphene citrate and gonadotrophins) or naturally conceived twins. All information about the women was recorded in a questionnaire designed for this study, completed in a face-to-face interview after obtaining verbal informed consent. Data were extracted into a computerized file that compared the following variables between the two groups: maternal age, gravidity, parity, pregnancy complications (pregnancy-induced hypertension (PIH) or preeclampsia, gestational diabetes mellitus (GDM), preterm premature rupture of membranes (PPROM), antepartum hemorrhage (APH) and anemia), gestational age at delivery, mode of delivery, birth weight, Apgar score, gross congenital abnormalities, sepsis, respiratory distress syndrome, neonatal intensive care unit (NICU) stay, and survival within the first week. Maternal complications included postpartum hemorrhage, blood transfusion, anemia and deep vein thrombosis (DVT).

Gestational age for ART-conceived twin pregnancies was calculated from the date of embryo transfer (11–13 weeks), and for non-ART-conceived pregnancies was calculated according to first trimester ultrasound estimation and/or last menstrual period [10]. The diagnosis of PIH was defined as blood pressure $>140/90$ mm Hg measured on two or more occasions after 20 weeks of gestation in previously normotensive women, with or without proteinuria (proteinuria of >100 mg/dL by urine analysis, or >300 mg/24 h) [11]. The diagnosis of GDM was based a fasting plasma glucose level of ≥ 5.6 mole/L or a 2 h plasma glucose level of ≥ 7.8 mole/L [12]. Antepartum hemorrhage was defined as any uterine bleeding episode during pregnancy not related to a non-obstetrical cause, such as cervical or vaginal lesions [13]. Pre-labor rupture of membranes referred to rupture of membrane with amniotic fluid without uterine activity [14]. Primary or secondary postpartum hemorrhage (PPH) was the loss of ≥ 500 ml blood from the genital tract within 24 h during the 12 weeks from birth [15]. Blood transfusion was performed (antepartum, intrapartum or postpartum) during management of massive APH and/or PPH from blood loss greater than 1000 ml and/or signs of clinical shock [16]. One case of DVT presented as pain and swelling of the left leg and was diagnosed by compression duplex ultrasound and a

D-dimer test; the patient was admitted for 1 week and supervised by an internal physician [17].

All neonates were evaluated by an expert neonatologist during the 1 week following birth. In our study, extreme preterm labor was defined as labor <28 weeks, and very preterm labor was 33 to 36 weeks of gestation. Late preterm was previously defined as labor between 32 to 36 weeks and 6 days of gestation [18], however, in our study late preterm was defined as 33–36 weeks, and term was over 37 weeks.

Birth weight was categorized as extreme low birth weight (LBW) for <1000 g, very LBW for 1000–1500 g, LBW for 1500–2500 g, and normal birth weight for >2500 g [18]. The Apgar score was classified as severely depressed $<0-3>$, moderately depressed $<4-6>$ and excellent condition $<7-10>$ [19]. Respiratory distress syndrome was defined as presence of a characteristic radiographic finding and the requirement of oxygen for 24 h. Sepsis was diagnosed using clinical criteria and laboratory tests [19].

Ethical Considerations

All pregnant women with diachronic twins were informed about the purpose of the study and verbal consent was obtained from all women in the study.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 22). Chi square test of association was used to compare proportions. Fisher's exact test was used when the expected count of more than 20% of the cells of the table was <5 . Student's t test of two independent samples was used to compare two means. A p value of ≤ 0.05 was considered statistically significant.

Results

Two hundred women with twin pregnancies participated in the study. The development of twin was spontaneous in 121 women, and iatrogenic in 79 women. Table 1 shows that the mean age (\pm SD) of women in the iatrogenic group (35.41 ± 4.84 years) was significantly higher than the mean age (31.18 ± 8.58 years) of women in the spontaneous group ($p < 0.001$). Around half (44.3%) of women in the iatrogenic group were primigravids, compared with 19.8% of women in the spontaneous group ($p < 0.001$). None of the women in the iatrogenic group had family history of twin, compared with 48.8% of women in the spontaneous group ($p < 0.001$).

Table 1: Basic characteristics of the study groups

	Spontaneous		Iatrogenic		Total		
	No.	(%)	No.	(%)	No.	(%)	p
Age							
< 25	32	(26.4)	1	(1.3)	33	(16.5)	
25-29	21	(17.4)	11	(13.9)	32	(16.0)	
30-34	21	(17.4)	19	(24.1)	40	(20.0)	< 0.001
35-39	19	(15.7)	32	(40.5)	51	(25.5)	
≥ 40	28	(23.1)	16	(20.3)	44	(22.0)	
Mean (+ SD)	31.18	(+8.58)	35.41	(+4.84)			< 0.001*
Parity							
Primiparous	24	(19.8)	35	(44.3)	59	(29.5)	
Multiparous	71	(58.7)	43	(54.4)	114	(57.0)	
Grand multiparous	26	(21.5)	1	(1.3)	27	(13.5)	
Mean (+ SD)	2.61	(+2.417)	0.84	(+0.966)			< 0.001*
Family history of twin							
Present	59	(48.8)	0	(0.0)	59	(29.5)	< 0.001
Absent	62	(51.2)	79	(100.0)	141	(70.5)	
Total	121	(100.0)	79	(100.0)	200	(100.0)	

*By t test for two independent samples.

Table 2 shows that 19% of women in the iatrogenic group had antepartum hemorrhage (APH) compared with 9.9% of women in spontaneous group, but the difference was not significant ($p = 0.067$). The rates of pregnancy induced hypertension (PIH), gestational diabetes (GDM), pre-labor premature rupture of membranes (PPROM) were significantly higher in the iatrogenic group compared with the spontaneous group ($p < 0.001$, $p < 0.001$, and $p = 0.015$ respectively). Regarding anemia, the rate in the spontaneous group (8.3%) was higher than that of the iatrogenic group ($p = 3.8\%$) but the difference was not significant ($p = 0.21$).

Table 2: Antenatal complications

Complications	No.	Spontaneous N = 121		Iatrogenic N = 79		Total N = 200	p
		(%)	No.	(%)	No.		
APH	12	(9.9)	15	(19.0)	27	(13.5)	0.067
PIH	3	(2.5)	31	(39.2)	34	(17.0)	< 0.001
GDM	1	(0.8)	18	(22.8)	19	(9.5)	< 0.001
PPROM	28	(23.1)	31	(39.2)	59	(29.5)	0.015
Anemia	10	(8.3)	3	(3.8)	13	(6.5)	0.21

Table 3 shows that the majority of women in the iatrogenic group delivered their first twin by CS (72.2%), while only 27.3% of women in the spontaneous group delivered by CS ($p < 0.001$). The main causes of CS in the whole sample were mal-presentation (25.6%) and previous lower segment CS (LSCS) (23.3%) but the differences were not significant between the two study groups regarding the causes of CS ($p = 0.246$). The same pattern can be applied for the second twin, as presented in Table 3.

Table 3: Mode of delivery and causes of CS in the two study groups

	Spontaneous		Iatrogenic		Total			
	No.	(%)	No.	(%)	No.	(%)	p	
MOD T1								
Vaginal	88	(72.7)	22	(27.8)	110	(55.0)	< 0.001	
CS	33	(27.3)	57	(72.2)	90	(45.0)		
Causes of CS T1								
Fetal distress	6	(18.2)	13	(22.8)	19	(21.1)	0.246*	
Mal-presentation	5	(15.2)	18	(31.6)	23	(25.6)		
Previous LSCS	8	(24.2)	13	(22.8)	21	(23.3)		
PIH	5	(15.2)	2	(3.5)	7	(7.8)		
Antepartum hemorrhage	3	(9.1)	4	(7.0)	7	(7.8)		
hemorrhage								
Elective LSCS	6	(18.2)	7	(12.3)	13	(14.4)	< 0.001	
MOD T2								
Vaginal	85	(70.2)	21	(26.6)	106	(53.0)		
CS	36	(29.8)	58	(73.4)	94	(47)		
Causes of CS T2								
Fetal distress	8	(22.2)	14	(24.1)	22	(23.4)	0.367*	
Mal-presentation	6	(16.7)	18	(31.0)	24	(25.5)		
Previous LSCS	8	(22.2)	13	(22.4)	21	(22.3)		
PIH	5	(13.9)	2	(3.4)	7	(7.4)		
Antepartum	3	(8.3)	4	(6.9)	7	(7.4)		
hemorrhage								
Elective LSCS	6	(16.7)	7	(12.1)	13	(13.8)		

*By Fisher's exact test. Note: T1=Twin 1; T2=Twin2

Table 4 shows that 21.5% of women of the whole sample developed post-partum hemorrhage (PPH), 25% needed blood transfusion, 31.5% developed anemia, and 0.5% developed deep venous thrombosis. No significant differences were detected between the two groups as presented in Table 4.

Table 4: Maternal Complications in the Two Study Groups

	Spontaneous N = 121		Iatrogenic N = 79		Total N = 200		
	No.	(%)	No.	(%)	No.	(%)	p
PPH	21	(17.4)	22	(27.8)	43	(21.5)	0.077
Blood transfusion	26	(21.5)	24	(30.4)	50	(25.0)	0.156
Anemia	36	(29.8)	27	(34.2)	63	(31.5)	0.51
DVT	1	(0.8)	0	(0.0)	1	(0.5)	1*

*By Fisher's exact test.

Table 5 shows, regarding the first twin, that the majority of women in the iatrogenic group delivered either extremely preterm (5.1%) or very preterm (72.2%) babies, compared with 12.4% and 25.6% respectively among women of the spontaneous group ($p < 0.001$). Same pattern is applied for the second twin ($p < 0.001$). In the spontaneous group, the birth weight of 49.6% of the first twins, and 43.8% of the second twins were normal, compared with only 15.2% and 11.4% respectively of twins in the iatrogenic group ($p < 0.001$). The rates of babies with excellent APGAR scores (in the first and fifth minutes) were significantly higher in the spontaneous group than in the iatrogenic group ($p < 0.001$).

Table 5: Neonatal outcomes of the two study groups

	Spontaneous		Iatrogenic		Total		p
	No.	(%)	No.	(%)	No.	(%)	
GA at delivery T1							
Extremely preterm	15	(12.4)	4	(5.1)	19	(9.5)	< 0.001
Very preterm	31	(25.6)	57	(72.2)	88	(44.0)	
Late preterm	62	(51.2)	18	(22.8)	80	(40.0)	
Term	13	(10.7)	0	(0.0)	13	(6.5)	
GA at delivery T2							
Extremely preterm	15	(12.4)	5	(6.3)	20	(10.0)	< 0.001
Very preterm	33	(27.3)	61	(77.2)	94	(47.0)	
Late preterm	60	(49.6)	13	(16.5)	73	(36.5)	
Term	13	(10.7)	0	(0.0)	13	(6.5)	
Birth weight T1							
Extremely LBW	19	(15.7)	6	(7.6)	25	(12.5)	< 0.001
Very LBW	4	(3.3)	8	(10.1)	12	(6.0)	
LBW	38	(31.4)	53	(67.1)	91	(45.5)	
Normal	60	(49.6)	12	(15.2)	72	(36.0)	
Birth weight T2							
Extremely LBW	18	(14.9)	9	(11.4)	27	(13.5)	< 0.001
Very LBW	6	(5.0)	9	(11.4)	15	(7.5)	
LBW	44	(36.4)	52	(65.8)	96	(48.0)	
Normal	53	(43.8)	9	(11.4)	62	(31.0)	
APGAR 1M-T1							
Severely depressed	16	(13.2)	3	(3.8)	19	(9.5)	< 0.001
Moderately depressed	41	(33.9)	67	(84.8)	108	(54.0)	
Excellent	64	(52.9)	9	(11.4)	73	(36.5)	
APGAR 1M-T2							
Severely depressed	18	(14.9)	12	(15.2)	30	(15.0)	< 0.001
Moderately depressed	46	(38)	60	(75.9)	(75.9)	(53.0)	
Excellent	57	(47.1)	7	(8.9)	64	(32.0)	
APGAR 5M-T1							
Severely depressed	11	(9.1)	3	(3.8)	14	(7.0)	< 0.001
Moderately depressed	30	(24.8)	43	(54.4)	73	(36.5)	
Excellent	80	(66.1)	33	(41.8)	113	(56.5)	
APGAR 5M-T2							
Severely depressed	10	(8.3)	5	(6.3)	15	(7.5)	< 0.001
Moderately depressed	36	(29.8)	54	(68.4)	90	(45)	
Excellent	75	(62)	20	(25.3)	95	(47.5)	
Total	121	(100)	79	(100)	200	(100)	

Note: T1=Twin 1; T2=Twin2

Table 6 shows that 3.5% and 3% of the first and second twins respectively had congenital malformations. The rate of malformation in the second twins (6.3%) of the iatrogenic group was significantly higher than the rate (0.8%) of the spontaneous group ($p = 0.036$).

The admission rate to neonatal care unit (NCU) was significantly higher in the iatrogenic group than in the spontaneous group ($p < 0.001$).

No significant differences were detected between the two groups regarding neonatal sepsis, respiratory distress syndrome (RDS), and survival, as presented in Table 6.

Table 6: Neonatal Outcomes of the Two Study Groups

	Spontaneous N = 121		Iatrogenic N = 79		Total N = 200		
	No.	%	No.	%	No.	%	p
Congenital malformations T1	3	2.5	4	5.1	7	3.5	0.438*
Congenital malformations T2	1	0.8	5	6.3	6	3	0.036*
NCU admission T1	57	47.1	62	78.5	119	59.5	< 0.001
NCU admission T2	58	47.9	62	78.5	120	60	< 0.001
Neonatal sepsis T1	25	20.7	12	15.2	37	18.5	0.33
Neonatal sepsis T2	26	21.5	21	26.6	47	23.5	0.406
RDS T1	42	34.7	33	41.8	75	37.5	0.313
RDS T2	45	37.2	40	50.6	85	42.5	0.06
Survival T1	92	76	64	81	156	78	0.406
Survival T2	91	75.2	51	64.6	142	71	0.105

*By Fisher's exact test. T1=Twin 1; T2=Twin2

Discussion

ART is being increasingly used worldwide in the treatment of infertility, and a consequence of it increased rate of use are twin pregnancies and associated complications. With improved obstetrical and neonatal care, the incidence of maternal and perinatal morbidity and mortality are decreasing. It is known that twin pregnancy is associated with a higher maternal and fetal risk. More women are undergoing ART, and we have observed inconsistent published findings regarding the pregnancy outcomes of women with twins from ART. Although some previous studies addressed similar issues, other studies have demonstrated comparable perinatal outcomes between the spontaneous and ART groups [8,14,21,22,23]. Some studies reported that among dichorionic twin pregnancies, where a fixed management protocol was applied, assisted conception was not associated with adverse perinatal or obstetric maternal outcomes [6, 5, and 22].

Age at delivery is increasing internationally, and this is associated with an increased use of ART. As expected, in our study we found that patients using ART were significantly older and exhibited a lower parity than those who conceived spontaneously. Many previous studies found increasing maternal age and null parity to be associated adverse perinatal outcomes [4, 22-26]. However, other studies found no association of age and previous parity with perinatal outcomes in any groups including nulliparous patients in these studies [3, 27, 28].

In our study, the rates of maternal complications, such as PIH, GDM and PPRM, were significantly higher in the iatrogenic group compared with the spontaneous group. While APH was higher in ART group, the difference was not significant. In contrast, anemia was higher in spontaneous group, but the difference was not significant. Other complications, such as PPH, blood transfusion, anemia, and DVT, showed no significant differences between the two groups.

Similar pregnancy complications were investigated in previous studies [20,25,26, 29,30]. Findings from the present study suggested that most maternal complications, such as PIH or preeclampsia, GDM, placental abruption, premature rupture of membranes, and postpartum hemorrhage, were higher in the ART compared with spontaneous group. Other studies showed these complications were similar in the two groups [31,26,32].

For neonatal outcomes, our study indicated that the risk of preterm birth, very preterm birth, LBW, congenital malformation, NCU admission rate, and moderately depressed Apgar scores (in the first and fifth min) were markedly higher in ART group than those conceived naturally. Previously, no significant differences were detected between the two groups regarding neonatal sepsis, RDS and survival [33-38]. In terms of neonatal outcomes, some studies showed that ART twin pregnancies were at greater risk of LBW, preterm birth, congenital anomalies neonatal respiratory distress syndrome, and perinatal mortality [4,39]. Some studies had similar neonatal outcomes, whereas other reports have suggested better neonatal outcomes after ART [2,7]. Our study found that the majority of women in the ART group delivered by CS, with mal-presentation the most common cause of CS, consistent with another study, and previous LSCS the second most common, followed by elective LSCS on maternal request [40,41]. Our study also supports the contention that the second twin has a poorer outcome than that of the first twin. This was evident whether the pregnancy was conceived spontaneously, after ovulation induction or ART. The reasons for the better first twin outcome is unknown and warrants further investigation.

Conclusion

Maternal and neonatal outcomes were poorer in the ART group. Maternal complications such as GDM, preeclampsia, significantly lower gestational age, birth weight and vaginal delivery rates were seen in ART pregnancies. The second twin has a poorer outcome, including lower birthweight, moderately depressed Apgar score, and more congenital anomalies compared with the first twin in both groups.

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