

## Outcome of Multiple Pregnancy Conceived Spontaneously Versus by Assisted Reproductive Therapy (Comparative Study)

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### Abstract

**Background:** There is a continuous controversy regarding the obstetric perinatal outcome of multiple pregnancies conceived after assisted reproductive techniques (ART). There is an ongoing discussion whether these parameters may show poorer results as compared to spontaneous conception.

**Aims:** of the present study were to compare the perinatal outcome in spontaneous multiple pregnancies compared to those conceived by ART and to design a booklet to orient the parturient women included in the study about spontaneously conceived and ART conceived multiple pregnancies.

**Design:** A prospective cohort observational study was used.

**Setting:** The study was conducted at the labor ward at labor and child hood hospital, Zagazig University hospital. **Subjects:** Group A consisted of 83 parturient women with spontaneously conceived multiple pregnancies and group B which consisted of 27 parturient women with multiple pregnancies conceived by ART who were admitted to the study setting within a period of one year from January to December, 2015.

**Tools:** Data collection tool consisted of 3 parts, structured interview questionnaire, labor record and neonatal record.

**Results:** Group B were significantly complicated with threatened abortion and placenta previa than group A (24.0% & 24.0% VS. 7.1% & 2.4% respectively). Premature rupture of membrane and severe preeclampsia were statistically significant main indications of emergency cesarean delivery in group A compared to group B, while placenta previa was a statistically significant main indication for emergency CS in group B compared to group A (P= 0.032). As regards neonatal outcome, there were a statistically significant increase in the neonatal intensive care unit admission and still birth in group B compared to group A (64.0% & 22.0% VS. 46.4% & 2.9% respectively).

**Conclusion:** Based on the findings of the study, When compared to spontaneously conceived twins, ART-conceived twins are more or less similar to those conceived spontaneously.

**Recommendation:** Multiple pregnancy in general whether conceived spontaneously or by ART techniques require proper antenatal, intra-natal and postnatal care as it poses several risks on both mother and fetus.

**Keywords:** Multiple pregnancy, spontaneous pregnancy, assisted conception, outcome.

### I. Introduction

When *in vitro* fertilization (IVF) was first introduced into clinical practice, there were no data available on its safety. The first reports on the safety of IVF were published by Cohen [1] and the American Society for Reproductive Medicine and Society of Assisted Reproductive Technology [2].

In recent years, an increasingly large proportion of deliveries following ART have been multiple pregnancies [3]. The most important reason for the increased rates of adverse perinatal outcomes observed in ART pregnancies is multifetal pregnancies. In addition, even in singleton pregnancies, ART may be associated with an increased risk of adverse perinatal outcomes, including increased rates of labor induction and Caesarean delivery. A small but significant increase in congenital structural anomalies and chromosomal abnormalities has also been observed in singleton ART pregnancies in studies including pregnancy terminations. [4,5]

Multiple gestational pregnancies are now recognized as a major epidemiological concern associated with both assisted reproductive technologies (ART) and ovulation induction therapies. Today by far the greatest number of multiple gestation pregnancies is due to some type of assisted procreation. The number of twins associated with ART has been estimated to be as high as 32% [6]

This trend has a great degree of importance to clinicians involved in assisted reproduction since studies have shown that not only is multiple gestations more common in ART conceptions, but that when compared to spontaneous conceptions (SC), ART conceptions have demonstrated a higher chance of detrimental effects for both mothers and neonates [7,8].

### II. Subjects and Methods

#### Research Design:

A prospective cohort observational study was used to achieve the aim of the current study.

**Aims of the study:** to compare the perinatal outcome in spontaneous multiple pregnancies compared to those conceived by ART and to design a booklet to orient the parturient women included in the study about spontaneously conceived and ART conceived multiple pregnancies.

**Setting:**

The current study was conducted at labor ward of labor and childhood hospital, Zagazig university hospitals.

**Subjects:**

The parturient women with multiple pregnancies at a period of one year from January to December 2015, were recruited in the study. The total number was (112) parturient women with multiple pregnancies and they were divided into two groups:

**Group A:** Consisted of ( 83) conceived spontaneously

**Group B:** Consisted of (27) conceived by one of the assisted reproductive technologies.

The researchers selected The parturient women with multiple pregnancies who met the following inclusion criteria: no medical disorders were encountered before pregnancy as diabetes mellitus, hypertension, heart disease, hepatic or renal disease.

**Tools of Data Collection:**

**1- Structured Interview Questionnaire:**

It included data related to age, parity, previous multiple pregnancy, medical and obstetric complications encountered during previous multiple pregnancy. It also included current pregnancy history as method of conception, type of the assisted reproductive technology used, number of fetus and current pregnancy complications.

**2- Labor Record:**

It included data related to the gestational age at the onset of delivery, the mode, route of delivery, types of CS and its indications and occurrence of postpartum hemorrhage.

**3- Neonatal Record:**

It included data related to each newborn as APGAR score at the 1<sup>st</sup> and 5<sup>th</sup> minute, need for resuscitation, birth weight, admission to NICU, gross congenital anomalies, still birth and neonatal death.

**Content Validity and Reliability:**

Tools were submitted to a panel of five experts in the field of maternity nursing and obstetrics medicine to test the content validity. Modifications were carried out according to the panel judgment. Reliability test was assessed by applying the tools on 10 women.

**Pilot Study:**

A pilot study was carried out on 10% of parturient women with multiple pregnancies and they were not included in the study sample to test the study tools in terms of clarity and feasibility and necessary modifications were done.

**Field Work:**

Data collection took a period of one year from January to December 2015. After getting the official permission, the pilot testing of the study tools was done and analyzed. The initial assessment was done by the on duty physician with the assistance of the researchers and the parturient women were allocated to either group A and group B afterwards. The delivery was conducted at labor and childhood hospital with the assistance of the on duty physician. The mode of delivery and any complications following delivery were assessed. Neonatal assessment was done through measuring the APGAR score and finding out any abnormality that needed admission to the neonatal intensive care unit.

**Administrative and ethical considerations:**

An official permission was obtained by submission of an official letter from the faculty of nursing to the responsible authorities of the study setting to obtain the permission for data collection. Nursing and medical staff responsible for the patients were approached to gain their cooperation. All ethical issues were taken into consideration during all phases of the study. The aim of the study was explained to every woman before participation, which was totally voluntary. Women were assured that the study maneuver will cause no actual or potential harm on them and professional help was provided whenever needed. Women were notified that they

can withdraw at any stage of the research; also they assured that the information obtained during the study will be confidential and used for the research purpose only.

**Statistical analysis:**

After collection of data, it was revised, coded and fed to statistical software SPSS version 16. The statistical analysis used T test with alpha error = 0.05. Microsoft office excel software was used to construct the needed graphs. After data coding the following data manipulations were done. After data manipulation was done all numeric data were expressed in the form of range (minimum to maximum), mean and standard deviation (SD). Categorical data were expressed in the form of frequencies and percentages.

**III. Results**

**Table 1) Distribution of the study subject according to age and obstetrics history**

Characteristics	Group				Total		MCP
	Spontaneous conception		Assisted conception		No	%	
	No	%	No	%			
<b>Age (years)</b>							0.001*
▪ <25	37	43.5	3	12.0	40	36.4	
▪ 25-35	41	48.2	14	56.0	55	50.0	
▪ 35+	7	8.2	8	32.0	15	13.6	
<b>Mean±SD</b>	<b>35.58±6.57</b>						
<b>Gravida</b>							0.001*
▪ Primigravida	26	30.6	18	72.0	44	40.0	
▪ 2-3	42	49.4	3	12.0	45	40.9	
▪ 4-8	17	20.0	4	16.0	21	19.1	
<b>Parity</b>							0.001*
▪ Nullipara	27	31.8	18	72.0	45	40.9	
▪ Primipara	29	34.1	6	24.0	35	31.8	
▪ 2-5	29	34.1	1	4.0	30	27.3	
<b>Abortion</b>							0.476!
▪ No	62	72.9	20	80.0	82	74.5	
▪ Yes	23	27.1	5	20.0	28	25.5	
<b>Previous multiple pregnancy</b>							
▪ Yes	13	15.3	1	4.0	14	12.7	
▪ No	72	84.7	24	96.0	96	87.3	

MCP: Mont Carlo exact probability !: Fisher exact probability \* P < 0.05 (significant)

Table 1) Shows comparison of age and obstetrics history among spontaneous and assisted conception groups, there were 8.2% of spontaneous group were more than 35 years compared to 32% in assisted conception group observed were a statistically significant. Regarding number of gravida, number of parity as majority of assisted conception group were primigravida and null parity (72%, 72% respectively).

**Table 2) Obstetric complications encountered during previous multiple pregnancy**

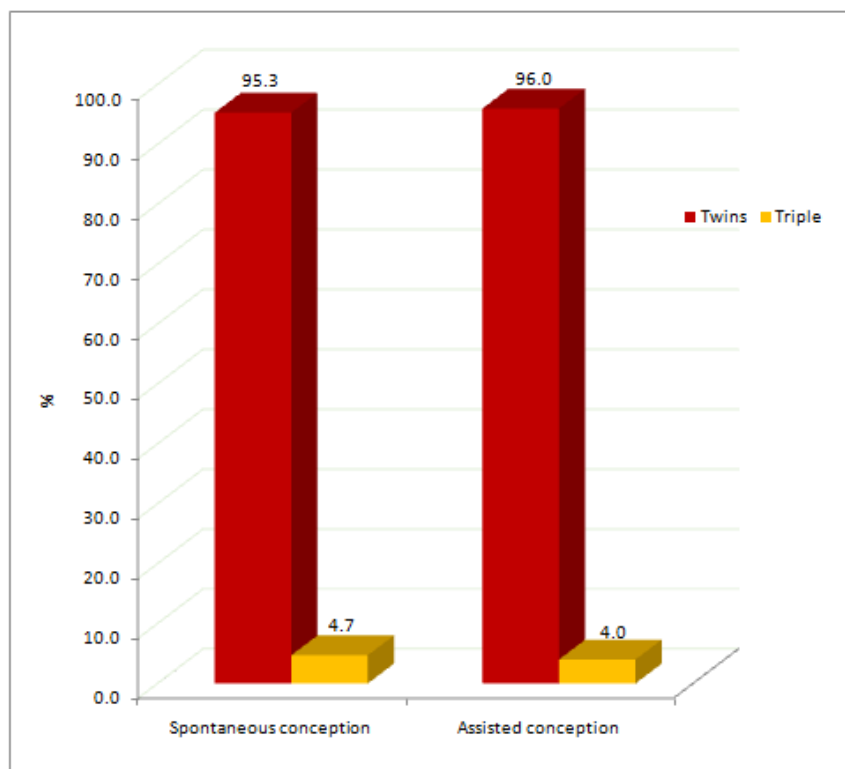
Obstetric complications encountered during Previous multiple pregnancy	Group				Total		FEP
	Spontaneous conception (n=13)		Assisted conception (n=1)		No	%	
	No	%	No	%			
<b>Previous multiple pregnancy</b>							0.136!
▪ Yes	13	15.3	1	4.0	14	12.7	
▪ No	72	84.7	24	96.0	96	87.3	
Threatened abortion	2	15.4	0	0.0	2	14.3	0.627
Oligohydramnios	2	15.4	0	0.0	2	14.3	0.627
Preeclampsia	1	7.7	0	0.0	1	7.1	0.773
Accidental He	1	7.7	1	100.0	2	14.3	0.521
Preterm labor	1	7.7	0	0.0	1	7.1	0.733
CS	6	46.2	0	0.0	6	42.9	0.369
Obstructed labor	1	7.7	0	0.0	1	7.1	0.773
PPH	2	15.4	0	0.0	2	14.3	0.627
Admission to NICU	2	15.4	0	0.0	2	14.3	0.672

!: Mont Carlo exact probability

As regard complication encountered during previous multiple pregnancy table 2 shows that 15.3% in spontaneous group reported previous multiple pregnancy compared to 4% in assisted conception group and non-statistically significant difference observed. between the two study group only one case in assisted conception

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group had accidental hemorrhage during their previous pregnancy this can be explained as majority of assisted conception group where primigravida.



**Figure 1)** Comparison between number of fetus in both spontaneous conception and assisted conception group.

Regarding number of fetus figure 1 illustrated no difference between spontaneous and assisted conception groups 95.3% compared to 96% respectively.

**Table 3)** Distribution of the study subjects according to complication encounter during present pregnancy and regularity of ANC

Current pregnancy complications	Group				Total		FEP
	Spontaneous conception		Assisted conception		No	%	
	No	%	No	%			
Threatened abortion	6	7.1	6	24.0	12	10.9	0.017*
Oligohydramnios	2	2.4	0	0.0	2	1.8	0.439
Preeclampsia	17	20.0	8	32.0	25	22.7	0.208
DM	6	7.1	3	12.0	9	8.2	0.427
Placenta previa	2	2.4	6	24.0	8	7.3	0.001*
Accidental He	2	2.4	0	0.0	2	1.8	0.439
IUFD	7	8.2	3	12.0	10	9.1	0.565
Preterm labor	4	4.7	2	8.0	6	5.5	0.524
IUGR	3	3.5	0	0.0	3	2.7	0.341
PROM	29	34.1	5	20.0	34	30.9	0.179
Regular ANC	48	56.5	25	100.0	73	66.4	0.001*
Hospital admission for pregnancy complications	22	25.9	11	44.0	33	30.0	0.050*

FEP: Fisher exact probability\* P < 0.05 (Significant)

Table 3 reveal that there is statistically significant difference between assisted and spontaneous conception group regarding complication encountered during present pregnancy, there were 24% & 24% of assisted group had threatened abortion and placenta previa respectively compared to 7.1% & 2.4% in spontaneous group.

As regard antenatal care 100% of women in assisted conception group were attended to ANC regularly compared to 56.5% in spontaneous group. Also 44% of assisted conception group admitted hospital for treatment of complication during pregnancy compared to 25.9% in spontaneous conception group and difference observed were statistically significant.

**Table 4)** Comparison of study subject according to mode of delivery

Labor data	Group				Total		MCP
	Spontaneous conception		Assisted conception		No	%	
	No	%	No	%			
<b>Mode of delivery</b>							0.740
▪ Normal vaginal delivery	21	24.7	7	28.0	28	25.5	
▪ Cesarean section	64	75.3	18	72.0	82	74.5	
<b>Type of CS</b>							0.050*
▪ Emergency CS	41	64.1	7	38.9	48	58.5	
▪ Elective CS	23	35.9	11	61.1	34	41.5	
<b>Indications of emergency CS</b>							0.032*
▪ Severe PET	13	31.7	1	14.3	14	29.2	
▪ Accidental He	1	2.4	0	0.0	1	2.1	
▪ Placenta previa	6	14.6	5	71.4	11	22.9	
▪ Oligohydramnios	2	4.9	0	0.0	2	4.2	
▪ PROM	15	36.6	0	0.0	15	31.3	
▪ Fetal distress	4	9.8	1	14.3	5	10.4	
<b>Indications of elective CS</b>							0.001*
▪ ART	0	0.0	8	72.7	9	26.5	
▪ Previous CS	12	52.2	0	0.0	12	35.3	
▪ Malpresentation	9	39.1	3	27.3	12	35.3	
▪ CPD	1	4.3	0	0.0	1	2.9	
<b>GA at the onset of labor</b>							0.162
▪ <37 wks.	42	49.4	17	68.0	59	53.6	
▪ 37-39	37	43.5	8	32.0	45	40.9	
▪ 40+	6	7.1	0	0.0	6	5.5	
<b>PPH</b>							0.970!
▪ Yes	7	8.2	2	8.0	9	8.2	
▪ No	78	91.8	23	92.0	101	91.8	

MCP: Mont Carlo exact probability      !: Fisher exact probability \* P < 0.05 (significant)

Distribution of study subject according to mode of delivery illustrated in table 4 astatically significant difference observed between the two study group as 61.1% of assisted conception group delivered by CS electively compared to 35.9% in spontaneous conception group.

Regard indication of C.S astatically significant difference observed between the two study groups as there were 71.4% and 52.2% of assisted conception group had placenta previa and previous CS as indication of CS respectively compared to 14.6% and 0.0% in spontaneous conception group respectively .

**Table 5)** Comparison of neonatal outcome between spontaneous and assisted conception group

Newborn data	Group				Total		X <sup>2</sup> (P)
	Spontaneous conception		Assisted conception		No	%	
	No	%	No	%			
<b>Maturity</b>							2.9 (0.635)
▪ Preterm	84	49.4	34	68.0	118	53.6	
▪ Full term	86	50.6	16	32.0	102	46.4	
<b>Resuscitation</b>							2.7 (0.529)
▪ Yes	92	54.1	33	66.0	125	56.8	
▪ No	78	45.9	17	34.0	95	43.2	
<b>Birth weight</b>							4.3 (0.507)
▪ <1500	34	20.0	16	32.0	50	22.7	
▪ 1500-2500	66	38.8	25	50.0	91	41.4	
▪ 2500+	70	41.2	9	18.0	79	35.9	
<b>NICU admission</b>	79	46.4	32	64.0	111	50.5	5.9 (0.028)*
<b>Congenital anomalies</b>	2	1.17	0	0.0	2	0.9	0.857!
<b>Stillbirth</b>	5	2.9	11	22.0	16	7.3	0.042*
<b>Neonatal death</b>	5	2.9	0	0.0	5	2.3	0.241!

!: Fisher exact probability \* P < 0.05 (significant)

Table 5 summarizes the distribution of the study subject according to neonatal outcome. In relation to maturity of neonate there 68% of neonate of assisted conception group were preterm compared to 49.4% of spontaneous conception group but difference observed statistically insignificant.

Regarding neonatal resuscitation there were no statistically significant difference between the two study group as 54.1% of spontaneous conception group need resuscitation compared to 66% assisted conception group. Also table 5 shows that there were a statistically significant observed between spontaneous and assisted conception group neonatal admission to NICU as 64% of assisted conception group admitted NICU compared to 46.4% in spontaneous group.

The same table also shows that there were a statistically significant observed between spontaneous and assisted conception group regarding stillbirth 22% of assisted conception group were stillbirth compared to 2.9% in spontaneous conception group.

#### IV. Discussion

The incidence of twins has markedly increased since the introduction of IVF/ICSI program. To epidemic proportions. International registries have documented this increase over time. In the 2002 report by the European Society for Reproductive Medicine (ESHRE), the distribution of singleton, twin and triplet deliveries for IVF and ICSI combined was 75.5, 23.2 and 1.3%, respectively, giving a total multiple delivery rate of 24.5% [9]. This was only a marginal improvement on the

2001 report, which demonstrated a 25.5% multiple delivery rates [10].

Aim of the present study was to compare the perinatal outcomes in spontaneous twins compared with those conceived by ART.

Statistically significant difference observed between the two studied groups regarding maternal age, and obstetric history there were 8.2% of spontaneous group were more than 35 years compared to 32% in assisted conception group observed were a. Regarding number of gravida, number of parity as majority of assisted conception group were primigravida and null parity. The results of the present study are in contrast with those reported by **Eskandar, M. 2007 [10]** who reported that There was no significant difference in the patients' age, relevant obstetric history with similar numbers of previous pregnancies (gravida) and deliveries (para).

As regard complication encountered during previous multiple pregnancy non-statistically significant difference observed between the two studied groups only one case in assisted conception group had accidental hemorrhage during their previous pregnancy as majority of them were primigravida.

Regarding complication encountered during present pregnancy, there is statistically significant difference between assisted and spontaneous conception group nearly one quarter of assisted group had threatened abortion and placenta previa respectively compared to 7.1% & 2.4% in spontaneous group. This finding was in agreement with **Baxi A, Kaushal M(2008)** who reported that pregnancy-related complications like antepartum hemorrhage, pregnancy-induced hypertension, gestational diabetes, and postpartum hemorrhage were similar in both the groups and were not statistically significant.

As regard antenatal care 100% of women in assisted conception group were attended to ANC regularly compared to 56.5% in spontaneous group. Also nearly half of assisted conception group admitted hospital for treatment of complication during pregnancy compared to one quarter in spontaneous and difference observed were statistically significant. In the same line **Luke et al. 2004** reported that assisted conception was not normally by itself a risk factor adverse outcome. Although in our study pregnancy complications in ART pregnancies are comparable with non-ART twin pregnancies, the ART twin mothers were more likely to be on sick leave or hospitalized during pregnancy. This could be because of increased anxiety and concern for the newborn.

According to mode of delivery a statistically significant difference observed between the two study groups as 61.1% of assisted conception group delivered by CS electively compared to 35.9% in spontaneous conception group. Regarding indication of C.S a statistically significant difference observed between the two study groups as there were 71.4% and 52.2% of assisted conception group had placenta previa and previous CS as indication of CS respectively compared to 14.6% and 0.0% in spontaneous conception group respectively.

This finding was in agreement with **Filicori Metal. 2005**. Reported that the overall cesarean delivery rate his study was high with the ART group having a higher rate than spontaneous group. Increased operative delivery in twin pregnancy has been defined in many studies. The cesarean birth rate in ART group was significant higher than that of spontaneous group.

Investigating relation to maturity of neonate there more than half of neonate of assisted conception group were preterm compared to 49.4% of spontaneous conception group but difference observed statistically insignificant.

This finding was in agreement with **Filicori Metal. 2005** who reported that the mean birth weight in ART twin pregnancy was significant lower than spontaneous conception. Preterm birth is a frequent problem in women who undergo treatment for infertility. Infertile women seem to have predisposition to giving preterm birth and low birth weight babies. Even singleton births resulting from ART are associated with an increased risk of low birth weight. [5,9]

In the same line **Eskandar, M. 2007 reported that** there was a trend toward preterm labor with ICSI twins than with naturally conceived twins but no significant difference between both groups regarding neonatal weight, Apgar score (A/S) and weight of the placenta. In addition, the post-natal/ neonatal period was similar in both groups. There was no difference in maternal outcomes in both groups.

Regarding neonatal resuscitation there were no statistically significant difference between the two study groups as 54.1% of spontaneous conception group need resuscitation compared to 66% assisted

conception group. Also a statistically significant observed between spontaneous and assisted conception group neonatal admission to NICU as 64% of assisted conception group admitted NICU compared to 46.4% in spontaneous group.

In the same line **Sutcliffe AG 2002** found that twins conceived by IVF are at significant higher risk for prematurity and associated neonatal morbidity and mortality than spontaneously conceived twins. Similarly **Daniel et al,2000** found that ART-conceived twin pregnancy is at greater risk than non-ART conceived one for pregnancy complications and adverse perinatal outcome.

There were a statistically significant observed between spontaneous and assisted conception group regarding stillbirth 22% of assisted conception group were stillbirth compared to 2.9% in spontaneous conception group. In the other hand **Baxi A, Kaushal M(2008)** reported that preterm labor (88.9% vs. 57.9%) was more common in study group ( $P < 0.05$ ). Mean gestational age at the time of delivery was less in ART twin pregnancy than spontaneous pregnancies ( $34.51 \pm 3.1$  vs.  $36.81 \pm 2.5$ ). A significant difference was seen between both groups with respect to the mode of delivery

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