

# Spontaneous Twin Pregnancies Versus Twin Pregnancies Conceived with Assisted Reproductive Technologies \*

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**OBJECTIVE:** To evaluate the differences between spontaneous and assisted reproductive technology (ART) conceived twin pregnancies in respects of gestational and neonatal outcomes.

**STUDY DESIGN:** The comparison was made between 52 twin pregnancies conceived by ART and 80 spontaneous twins, delivered between years 2002 and 2004. Statistical analysis was performed by the SPSS program, version 11.5.

**RESULTS:** Rates of nulliparity, preterm labor, incidence of caesarean section, hospitalization time and neonatal mortality were significantly higher in the ART group. ART itself was not a risk factor for specific pregnancy complications such as pregnancy-induced hypertension, gestational diabetes mellitus and premature rupture of membranes. Gestational age at delivery, the birth weights of both the first and second twins were comparable between the groups.

**CONCLUSION:** ART conceived twin pregnancies pose the neonate to higher risks of complication related to morbidity and mortality than spontaneous twin pregnancies. Maternal morbidity rate was equal in both groups.

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**Key Words:** Twin pregnancy, Assisted reproductive technology, Perinatal mortality, Morbidity, Pregnancy outcome

Twin pregnancy is a risky type of pregnancy with high incidence of maternal and neonatal complications. As assisted reproductive technologies (ART) improved during the last decade, multiple pregnancies increased in number. Many unfavorable obstetric and neonatal outcomes such as pregnancy-induced hypertension (PIH), placenta previa, preterm delivery, cesarean section, low birth weight and small for gestational age (SGA) infants are also increased with ART.<sup>1,3</sup> The explicit reason of the less favorable results is unknown. However, one of the principal explanations that have been given for this unfavorable outcome is the high incidence of multiple pregnancies conceived by ART.<sup>4-7</sup>

There are not much data comparing the prognosis of twin pregnancies of ART and spontaneous ones. In the present study, we aimed to compare the perinatal and maternal outcome of ART conceived twin pregnancies with spontaneous twins.

## Material and Methods

Perinatal database of a university hospital was analyzed retrospectively for twin pregnancies delivered between 2002 and 2004. The comparison was made between ART and spontaneous twin pregnancies. ART methods included conventional in-vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and gamete intrafallopian transfer (GIFT).

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Non ART methods included the spontaneous and intrauterine insemination (IUI) pregnancies. Neonates who required intensive care treatment were admitted to the neonatal intensive care unit (NICU) of the same university hospital.

Gestational age was calculated by adding 14 days to the day of ovum pick-up as the week of amenorrhea for the ART group. For the spontaneous conception groups, the date of the last menstrual period or the fetal measurements obtained during the first trimester by ultrasonographic examination was used.

Diagnosis of pregnancy induced hypertension was defined as persistent blood pressure of  $>140/90$  mmHg after 20 week gestation in previously normotensive women. If proteinuria accompanied to the pregnancy induced hypertension, diagnosis of preeclampsia was made.

Threatening preterm labor is diagnosed when persistent uterine contractions are accompanied by a change in the cervix. Cervical sonography and a tocometer are also used during the diagnosis of cervical changes such as shortening of cervix and uterine contractions. Preterm birth was considered whenever the labor occurred before the end of the 37 weeks of gestation.

Diagnosis of gestational diabetes mellitus was based on a three hour 100-gram oral glucose tolerance test. In addition, the following definitions were used. Small for gestational age was defined as a birth weight below the 10<sup>th</sup> percentile for the gestational age. Intrauterine growth retardation was diagnosed as an ultrasonographic estimation of fetal weight below the 3<sup>rd</sup> percentile for the gestational age.

The birth weight discordance between the twins was defined as a  $>25\%$  difference in birth weights.

Table 1. Maternal characteristics in respect of age and parity

	ART twins	Spontaneous twins	
Number (n)	52	80	
Mean maternal age (year)(±SD)	31±4.3	28±4.8	P <0.001
Women >35 years % (n)	23.1 (12/52)	12.5 (10/80)	P=0.062
Nulliparous % (n)	90.3 (47/52)	55.0 (44/80)	P <0.001
Primiparous % (n)	9.6 (5/52)	26.3 (21/80)	P <0.001

Table 2. Maternal complications between groups

	ART twins	Spontaneous twins	
Number (n)	52	80	
PIH* and preeclampsia % (n)	9.6 (5/52)	8.8(7/80)	Not significant
GDM † % (n)	3.8 (2/52)	5.0 (4/80)	Not significant
Threatening preterm labor % (n)	28.8 (15/52)	15.0 (12/80)	P<0.05
Diabetes Mellitus % (n)	3.8 (2/52)	3.8 (3/80)	Not significant
PROM ‡ % (n)	13.5 (7/52)	17.5 (14/80)	Not significant
Discordant growth % (n)	3.8 (2/52)	12.5 (10/80)	P=0.052
Intrauterine fetal death % (n)	0	6.3 (5/80)	P=0.06
Febrile morbidity % (n)	3.8 (2/52)	3.8 (3/80)	Not significant
Hospitalization (day)	11.1±10.8	7.3±6.1	P<0.001

\*: PIH: Pregnancy Induced Hypertension

† GDM: Gestational Diabetes Mellitus

‡ PROM: Premature Rupture of Membranes

Table 3. Mode of delivery

	ART twins	Spontaneous twins	
Number (n)	52	80	
Cesarean section rate %(n)	94.2 (49/52)	68.8 (55/80)	P<0.01
Vaginal delivery rate %(n)	5.8 (3/52)	31.3 (25/80)	P<0.01

Table 4. Neonatal outcome between groups

	ART twins	Spontaneous twins	
Number (n)	52	80	
Gestational age at delivery (week)	34.4±2.7	34.5±3.7	Not Significant
Birth weight (g) 1st twin	2175±571	2123± 678	Not Significant
Birth weight (g) 2nd twin	2143±734	2014±629	Not Significant
NICU* admission 1st twin % (n)	19.2 (10/52)	31.3 (25/80)	P <0.001
NICU* admission 2nd twin %(n)	23.1 (12/52)	31.3 (25/80)	P <0.001
Neonatal death 1st twin % (n)	7.7 (4/52)	2.5 (2/80)	P <0.001
Neonatal death 2nd twin % (n)	11.5 (6/52)	2.5 (2/80)	P <0.001

\*: NICU: Neonatal Intensive Care Unit

First and fifth minute apgar scores were evaluated by a pediatrician who accompanied each birth. Records of the neonates, admitted to the neonatal intensive care unit were collected. The neonatal death included death during the first week following birth (early neonatal death).

Statistical analysis was performed by the  $\chi^2$ , Fisher exact tests. The two-tailed Student t-test and the one way analysis of variance (ANOVA) were used to compare groups' mean values. Significance was assumed if the p value is <0.05.

## Results

The study included 132 twin deliveries. The study group was composed of 52 pregnancies conceived by ART, and the control group consisted of 80 twin pregnancies obtained by non-ART methods.

Mean maternal age was 31±4 years (range: 17-43) in the study group and 28±4.8 in control group (P <0.001). The number of women, older than 35 years of age, were higher

in the study group (n=12) than that in the control group (n=10) (23 % versus 12.5 %)

The percentage of nulliparity was significantly higher among pregnancies conceived by ART than in those conceived spontaneously (90 % versus 55% respectively) ( $P < 0.001$ ) (Table 1).

As a complication of the pregnancy, premature rupture of membranes was seen in seven pregnancies of the ART group and 14 of the non ART group but this difference is not significant ( $P > 0.05$ ). (Table 2)

The comparison of the two groups in respect of threatening preterm labor reveals a higher number in the ART group (29% versus 15%) which is statistically significant ( $P < 0.05$ ).

The percentage of women who had specific pregnancy complications such as pregnancy induced hypertension, preeclampsia, gestational diabetes mellitus, were all comparable between the groups and we did not find any statistically significant difference ( $P > 0.05$ ).

Discordant growth was detected more commonly in non ART twins than in the ART group: 12.5% and 3.6% respectively ( $P = 0.052$ ).

There wasn't any intrauterine fetal death in ART group; whereas five intrauterine fetal deaths (5.8%) were seen in the control group ( $P = 0.06$ ).

94.5% (49/52) of the ART pregnancies ended with caesarean section, whereas in the control group the caesarean delivery rate was 69.2%. There is a statistically significant difference between the two groups ( $P < 0.001$ ). (Table 3)

Although the rate of caesarean section was higher in the study group, the incidence of maternal complications such as febrile morbidity (3.6% for the study group, 4.2% for the control group) was comparable between the groups (Table 2).

The percentages of vertex presentation for the study and control groups were 23.4%, 76.8% respectively.

The mean hospital stay including the pregnancy and the post delivery periods, for the ART group was  $11.1 \pm 10.8$  days and  $7.3 \pm 6.1$  days for the control group which is statistically significant. ( $P < 0.01$ )

The mean gestational age at delivery was  $34.41 \pm 2.7$  weeks in study group and  $34.5 \pm 3.77$  weeks in control group with no statistically significant difference ( $P > 0.05$ ). (Table 4) The mean birth weights of both the first and second twins were similar.

The first and fifth minute apgar scores for the study group were  $6.4 \pm 2.6$  and  $7.2 \pm 1.8$  and those for the control group were  $6.2 \pm 2.8$  and  $7.1 \pm 2.1$  respectively. The first minute apgar scores for the first and second twins were  $6.6 \pm 2.5$  and  $6.0 \pm 2.9$  respectively. The fifth minute values for the first and second twins were  $7.4 \pm 1.7$  and  $7.0 \pm 2.2$  respectively. The difference between Apgar score values of each group was similar.

Significantly less number of neonates in the study group were admitted to neonatal intensive care unit than those of the control group; 20% versus 31.9% for the first neonates and 23% versus 31% for the second neonates, respectively ( $P < 0.001$ ).

Neonatal mortality rate was higher in the study group than in the control group; 7.3% versus 2.5% for the first twin and 10.9% versus 2.5% for the second twin respectively ( $P < 0.001$ ). There were 6 fetal demises for the first twin and there were 8 fetal demises for the second twin.

## Discussion

Some studies noted that subfertility causes could have a negative effect even after adjusting for age, parity and multiplicity, and infertility itself could increase the risk for small for gestational age and preterm birth.<sup>8</sup> However, Oliviennes et al. in their retrospective study observed that risk of adverse perinatal outcome was not increased in twin pregnancies obtained after in vitro fertilization compared to spontaneous twins.<sup>9</sup>

The outcome of twin gestations resulting from ART has been a subject of controversy<sup>10</sup>. In the present study, we compared the ART conceived twin pregnancies with spontaneous ones. Moise et al. performed a case control study including 40 IVF twins and matched spontaneous ones.<sup>11</sup> Results of this clinical study revealed a shorter gestational age, higher rates of prematurity and a lower mean birth weight among the IVF pregnancies. Tallo et al. found similar results in a study with 68 IVF twins.<sup>12</sup>

In our study any significant relationship between prematurity and ART conceived twin pregnancies were not defined ( $P > 0.05$ ) (Table 4). Oliviennes et al. also did not find any difference between the rates of prematurity in twin pregnancies obtained after IVF and spontaneously conceived twins.<sup>9</sup>

In this study, we found a statistically significant difference in the mean age of women between the two groups and nulliparous women were more frequent in ART conceived group. Since most of the IVF patients spent many years to have a spontaneous pregnancy, this finding is expected. Kessler et al. found that patients undergoing IVF generally are older and nulliparous, which can affect the prevalence of obstetric complications.<sup>13</sup>

We found no statistically significant difference in the birth weights of twins and mean gestational age between the two groups. Our data were comparable with those of Lipitz et al. compared triplets conceived after IVF with spontaneous triplets and found no difference in gestational age and birth weight between the three groups.<sup>14</sup> Petersen et al. also concluded that birth weights of twins and triplets were not significantly different between IVF and control groups.<sup>15</sup>

There was a statistically significant difference in the admission to intensive care unit between the groups. ART conceived twins were less frequently admitted in neonatal care unit: 20% versus 31.9% for the first twin; 23% versus 31% for the second twin (Table 4).

We found that the neonates of the ART pregnancies stay longer in the neonatal intensive care unit. Although Bernoska et al. reported a significant birth weight difference between two groups; the neonatal outcome was similar.<sup>16</sup> Our results correlate with Bernoska in respect of general neonatal outcome. Probably the fact can be explained by close antenatal follow up and fast application of required procedures to an ART pregnancy and we speculate that the contributory effect of method of conception to perinatal outcome is not significant.

In this study, we found that ART was not a risk factor for specific pregnancy complications such as PIH, GDM and PROM. In contrast to our study, Liang et al. compared 104 ART twins with 173 spontaneous twins and showed higher incidence of these specific complications in the ART group.<sup>17</sup>

There was a significant difference between the types of deliveries between the groups. The cesarean section was more common in the ART group. Maternal anxiety among the ART pregnancies could be an influencing factor. It may also come from an attempt of the obstetrician to avoid any adverse outcome in a precious pregnancy.

Hospitalization duration was significantly longer in the study group. Hospital stay increases corresponding to the cesarean delivery and it might also be influenced by the complications of pregnancy such as threatening preterm labor which needs tocolytic treatment and hospitalization.

The rate of threatening preterm labor was also higher in the ART group. Preterm labor is four times more frequent in multiple pregnancies than singletons' and 50% of twins born prematurely.<sup>11,18</sup>

In conclusion, our current study suggests that ART conceived twin pregnancies do not have higher risks to the mother than non ART conceived pregnancies do but the risks to the neonate seems to be higher in respect of mortality. Since twinning itself is a risk factor both to the mother and to the neonate, special care should be given to all ART and non ART twins.

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