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ORIGINAL ARTICLE

## Multifetal gestations with assisted reproductive technique before the single-embryo transfer legislation: obstetric, neonatal outcomes and congenital anomalies

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### Abstract

**Objective:** To compare perinatal, neonatal outcome and congenital anomalies of multiple gestations conceived by means of assisted reproductive techniques with spontaneously conceived multiples before the limitation of number of embryo transfer.

**Methods:** Cases consisted of assisted reproductive technique (ART) multifetal gestations and control group comprised of spontaneously conceived multifetal gestations delivered in the same time period. Outcomes were perinatal, neonatal outcome, long-term outcomes and congenital anomalies of multiple gestations. There were 270 multifetal pregnancies for analysis, of which 137 were achieved by ART and 133 were spontaneous in this prospective study.

**Results:** Incidences of preeclampsia, gestational diabetes, deep vein thrombosis, thrombocytopenia, intrahepatic cholestasis and preterm premature rupture of membranes were similar in ART and spontaneous groups. There was no difference in fetal malformation rates between ART and control group, but higher rates of central nervous system malformation were observed (4 (1.5%) in control, 0 in ART group,  $p = 0.04$ ) in spontaneous group. No difference was seen in the perinatal mortality.

**Conclusions:** Neonatal and maternal outcomes are comparable between ART and spontaneous multifetal gestations. Congenital fetal malformation rates between ART and spontaneous multifetal pregnancies were similar except central nervous system malformation that was more likely in spontaneously conceived ones.

### Keywords

Assisted reproductive technique, multifetal gestations, quadreplet, triplet, twin

### History

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### Introduction

After the widespread use of assisted reproductive techniques (ART), concerns started to grow regarding congenital anomalies and the potential for associated obstetric outcomes. Higher incidences of prematurity, low-birth weight (LBW) and birth defects for children conceived following ART have been reported but this is ascribed mainly to the high incidence of multiple pregnancies that are compounded by a higher rate of perinatal morbidity and mortality [1–3]. A number of studies have shown higher prevalence of birth defects and neurological sequela in children born as a result of an IVF procedure [2,4,5]. Although some attribute this to the fact that this procedure involves a higher incidence of multiple fetus pregnancies, they have shown a risk for this phenomenon in singleton pregnancies as well [6]. Rates of multiple gestations associated with ART have been cited as high as 15–30% [7].

Because of the risk of multiple gestations, in March 2010 the Turkish Ministry of Health legislated to make single embryo transfer (SET) mandatory (for the first 2 IVF cycles) for women in Turkey who are aged 35 years and younger.

Several studies investigating the outcome of twin pregnancies conceived by IVF and OI have been conducted. However, these have shown conflicting results. Some studies have reported higher prematurity rates, lower birth weights and higher prenatal mortality in IVF twin pregnancies [8,9]. However, some investigators have found no differences in perinatal outcomes [6,10]. In contrast Fitzsimmons et al., have reported better outcomes in ART twin pregnancies [11]. These contradictory findings might be explained with absence of matching for maternal age and parity, differences in study design and combining the multiple gestations with singletons in same study population.

Counseling about the risks and outcomes of multiple gestations should be provided to patients who undergo ART. The information provided may have implications for decisions surrounding fetal reduction. The purpose of this prospective study was to compare perinatal, neonatal outcome, long-term

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outcomes and congenital anomalies of multiple gestations (twins, triplets and quadruplets) conceived by means of ART (IVF, ICSI) with spontaneously conceived multiples before the single-embryo transfer legislation. Analysis of umbilical artery blood gases, congenital anomalies and relatively long term outcomes of twins, triplets, quadruplets and outcomes of multifetal reductions might add further information to the current literature.

## Methods

All multifetal pregnancies that delivered at least 25 weeks of gestation from July 2007 until July 2010 at Istanbul University, Istanbul Medicine Faculty, a tertiary perinatal and reproductive medicine center, were analyzed. Approval for this prospective study was obtained from the Ethics Committee of the Institution.

Cases consisted of assisted reproductive technique (ART) multifetal gestations and a control group comprised of spontaneously conceived multifetal gestations delivered in the same time period. Women who underwent ovulation induction only, selective fetal termination, vanishing twin, cases which chorionicity was obscure, incomplete clinical follow-up and data, and women with underlying maternal disease that may have increased the risk of specific pregnancy complications (such as hypertension, diabetes, renal and liver diseases) were excluded. The data included women who underwent multifetal fetal reduction in both groups in order to interpret current clinical practice. Data of maternal age, paternal age, parity, mode of delivery, mode of conception, obstetric complications (vaginal hemorrhage, preterm premature ruptures of membranes (PPROM), hypertensive diseases of pregnancy, liver diseases, hematological diseases) were extracted from maternity records. To reduce the possible effect of maternal age, initially each ART multifetal pregnancy was matched to one spontaneous multifetal pregnancy by age ( $\pm 3$ ). Owing to exclusion of cases in spontaneous multiple pregnancy group, effort for proper matching was broken down.

Gestational age at delivery, birth weight, admission to neonatal intensive care unit (NICU), Apgar scores, umbilical arterial blood gases, growth restriction, mode of delivery, placentation, congenital abnormality, pregnancy complications (such as preeclampsia, gestational diabetes, PPRM) were recorded. The same study protocol was applied to identify and recruit patients, collect and interpret data, and to compare outcomes. Thus, the effect on results caused by inter-unit differences in data ascertainment and interpretation were minimized. All major congenital malformations, recognized during antenatal or neonatal period were reported.

Identification of two separate placentas was diagnostic of dichorionic pregnancy but it might be difficult in two adjacent placentas. Visualization of the intertwine membrane excludes monoamniotic placentation. Chorionicity can be determined by visualizing the extra-embryonic celomic space, in first trimester. Chorionicity can also be reliably determined by the presence or absence of the “twin peak” or “lambda” sign. Gestational age at birth was defined by adding 14 days to the day of ovum pick up as the week of amenorrhea for ART group. For the spontaneous multifetal pregnancies, the

gestational age based on known menstrual period if this was within 7 days of first trimester ultrasound derived estimate. When discrepancy was greater than 7 days, the ultrasound estimate was used. Between 20 and 23 weeks’ gestation a detailed fetal anatomic survey was performed by the experienced perinatologist at the same clinic.

A neonate was considered small for gestational age when birth weight was less than the 10th percentile for gestational age based on twin norms. Discordant birth weight was defined as greater than 20% difference in birth weight.

Maternal characteristics were compared by X<sup>2</sup> or two tailed Fisher exact test if the expected cell frequencies were small. Continuous variables were assessed by Student t test or Mann–Whitney U test for non-parametric variables. Neonatal outcomes were analyzed per twin pair (i.e. an adverse outcome was considered to be present if either one or both twins were affected). Statistical evaluations were performed using IBM SPSS version 21 (IBM Statistics, Chicago, IL).

## Results

A total of 297 multifetal pregnancies delivered over the study period. Twenty-seven of these were excluded because they were abortions, vanishing twin, fetoscopic laser application to twin-to-twin transfusion syndrome (TTTS), and/or incomplete data and clinical follow-up. There were 270 multifetal pregnancies for analysis, of which 137 were achieved by ART and 133 were spontaneous. There were 3 (2.2%) quadruplets, 22 (16.1%) trichorionic triamniotic triplets, 6 (4.4%) monochorionic diamniotic and 106 (77.4%) dichorionic diamniotic twins in ART group. Fetal reduction to twin performed to all of the three quadruplets without any complication. Eleven of 22 triplets had fetal reduction to twin and 11 (50%) carried over as triplets. In spontaneous conception group 3 of 6 triplets had fetus reduction to twin. There were 1 (0.8%) monochorionic monoamniotic twin and 41 (30.8) monochorionic diamniotic twins were analyzed in spontaneous group. Distribution of multifetal pregnancies shown in Figure 1. Mean maternal age was  $31.4 \pm 4.8$  (18–41) in ART group and  $28.8 \pm 4.9$  in spontaneous group. The mean number of transferred embryo was  $2.98 \pm 0.07$  in ART group. Most of cycles were ICSI (56.2%) and most of embryo cultured 3 days (72.3%) in a ready to use commercially available medium; IVF medium (Irvine Scientific, Santa Ana, CA). Clinical and laboratory characteristics of ART multifetal pregnancies are shown in Table 1.

The incidence of maternal morbidities is shown in Table 2. In our study we noted a non-significant increase in overall maternal complications in ART group. Incidences of preeclampsia, gestational diabetes, deep vein thrombosis, thrombocytopenia, intrahepatic cholestasis and PPRM were similar in ART and spontaneous groups. All maternal complications were treated according to treatment protocol of our clinic.

The results of neonatal outcomes are presented in Table 3. The mean gestational age at delivery was  $34.7 \pm 3$  weeks versus  $34.8 \pm 2.6$ , preterm delivery rate at  $<34$  weeks’ of gestation was 33.8% versus 34.6% and preterm delivery rate at  $<28$  weeks’ of gestation was 8.1% versus 3.8% ( $p = 0.1$ ) in the ART and spontaneous groups, respectively.

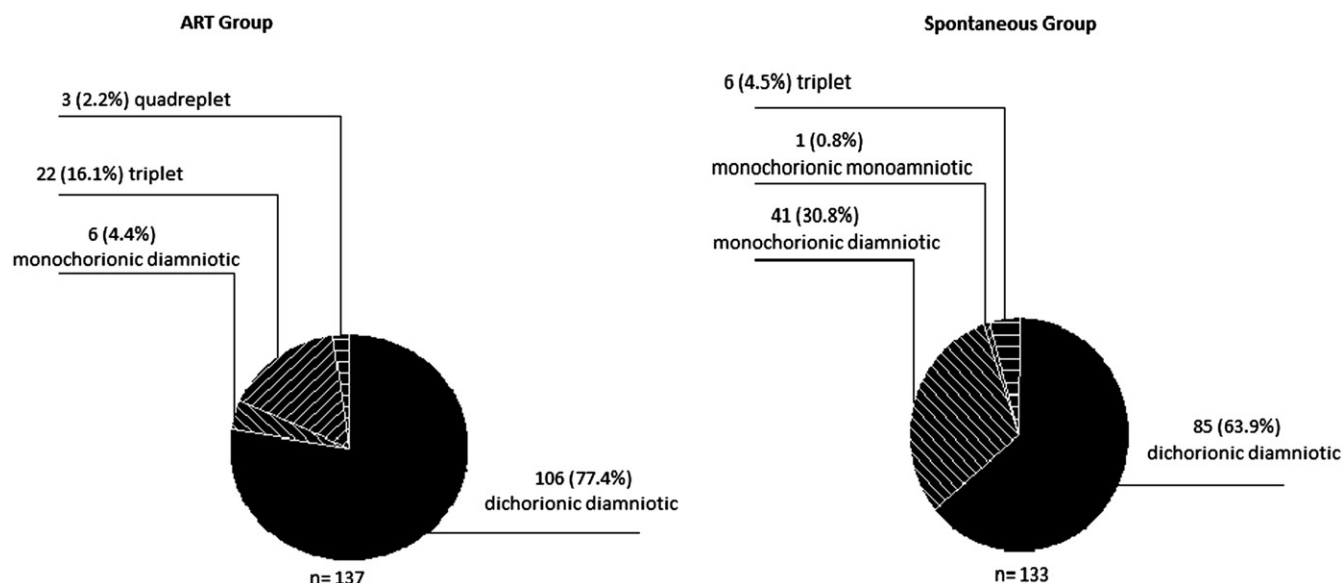


Figure 1. Distribution of multifetal pregnancies according to zygosity and chorionicity.

Table 1. Clinical and laboratory characteristics of ART multifetal pregnancies.

	Number (%)
Diagnosis	
Male	58 (42.3)
Unexplained	57 (41.6)
Female	32 (16.1)
Mode of ART	
IVF	60 (43.8)
ICSI	77 (56.2)
Cycle type	
Fresh	128 (93.4)
Frozen	9 (6.6)
Embryo transfer day	
Day 2	38 (27.7)
Day 3	99 (72.3)
Number of transferred embryos	
1	1 (0.7)
2	17 (12.4)
3	104 (75.9)
>3	15 (10.9)

ART: artificial reproductive technique, IVF: *in-vitro* fertilization, ICSI: intracytoplasmic sperm injection.

No differences in birth weight were seen. Also there was no difference in the proportion of babies who weighted <2500 g (low-birth weight) or <1500 g (very low-birth weight) in the two groups. Six (14.6%) TTTS developed in 41 spontaneous monochorionic diamniotic twins, however, all of cases in Quintero 1 stage required no intervention. No TTTS was observed in six monochorionic ART twins.

Admission rates to the NICU and mean number of days in NICU were similar in both the groups. There were three stillbirths in ART group. Two of them were due to fetal malformation of twin pair, and one occurred in one of the triplets. One stillbirth in control group was seen in one of the triplets, then the pregnancy completed without any complication. Perinatal mortality rate was not significantly higher in ART group. Fourteen babies (12 single of twins and 1 both pair) in ART group and 9 babies in spontaneous group died in

NICU because of prematurity related sepsis, intracranial hemorrhage, necrotizing enterocolitis and respiratory distress.

Assessment of the neonatal at birth revealed no differences in Apgar score of <5 at 1 min or <7 at 5 min in the ART and control groups. For the detection of asphyxia umbilical arterial blood gases were analyzed. Mean pH was  $7.31 \pm 0.06$  and mean base excess  $-2.8$  in ART group,  $pH 7.30 \pm 0.07$  and base excess  $-3$  in control group. When we use <7.26 to define acidosis, 13.6% of babies in ART group and 13.2% ( $p=0.9$ ) in spontaneous conception group were acidotic. Umbilical arterial  $pH < 7.05$  is defined as severe acidosis and we reported 1 in ART group and 4 in control group ( $p=0.4$ ).

Amniocentesis was performed for six women in ART group and four women in spontaneous conception group, because of high nuchal translucency measurement in first trimester. Trisomy-18 determined in one fetus in ART group and one trisomy-21 diagnosed in spontaneous group. Distribution of major fetal anomalies is presented in Table 4. There was no difference in fetal malformation rates between ART and control group, but higher rates of central nervous system malformation were observed (4 in control, 0 in ART group,  $p=0.04$ ) in spontaneous group. Anomalies were neural tube defect, hydrocephaly and ventriculomegaly. Mean postnatal follow-up was 27.6 months and mean breast feeding duration was 8.1 months. During follow-up period 10 (3.7%) children in ART and 5 (1.9%) in control group had a developmental deficit. One case in ART and 4 cases in spontaneous group had neurological problems during the follow-up.

## Discussion

The increased rate of multifetal pregnancies seen in recent years has been attributed to ART. Therefore it becomes very convenient to determine whether ART multifetal pregnancies are at increased risk of poor perinatal and obstetric outcomes compared with spontaneous multifetal gestations. Several reports investigating the outcome of multifetal gestations conceived by ART have been conducted. However, these have

Table 2. Distribution of maternal morbidities in multifetal pregnancies.

	ART multifetal gestations (n = 137)	Spontaneous multifetal gestations (n = 133)	p values
Maternal morbidity (n,%)	59 (46.5%)	46 (34.6%)	0.05
Preeclampsia (n,%)	13 (9.5%)	11 (8.3%)	0.7
Gestational diabetes (n,%)	22 (16.1%)	20 (15%)	0.8
Thrombosis (n,%)	3 (2.2%)	1 (0.8%)	0.6
Trombocytopenia (n,%)	8 (5.8%)	9 (6.8%)	0.8
PPROM (n,%)	6 (4.4%)	3 (2.3%)	0.3
Cholestasis (n,%)	3 (2.2%)	4 (3%)	0.7

ART: artificial reproductive technique, PPRM: preterm premature rupture of membranes.

Table 3. Neonatal outcomes of multifetal gestations.

	ART multifetal gestations	Spontaneous multifetal gestations	p values
Gestational age at birth†	34.7 ± 3 (26–39)	34.8 ± 2.6 (26–39)	0.7
<28 weeks of gestation†	11 (8.1%)	5 (3.8%)	0.1
<34 weeks of gestation†	46 (33.8%)	46 (34.6%)	0.9
>37 weeks of gestation†	50 (36.8%)	42 (31.6%)	0.4
34–37 weeks of gestation†	40 (29.4%)	45 (33.8%)	0.4
Prenatal mortality			
Antepartum†	3 (2.2%)	1 (0.8%)	0.3
One of twin	2	0	
One of triplets	1	1	
Intrapartum mortality	0	0	
Postpartum mortality†			0.2
One of twin	12 (8.8%)	3 (2.3%)	
Both of twin	1 (0.7%)	3 (2.3%)	
Apgar score at 1. min ≤ 7†	39 (15.5%)	32 (12.3%)	0.3
Apgar score at 5. min ≤ 7†	13 (5.2%)	8 (3.1%)	0.2
Apgar score at 1. min ≤ 5†	28 (11.1%)	26 (10%)	0.7
Apgar score at 5. min ≤ 5†	9 (3.3%)	3 (1.1%)	0.07
Discordance twin†	32 (23.4%)	32 (24.1%)	0.9
NICU admission†	112 (42.7%)	104 (43.3%)	0.9
NICU Stay (day)†	26.3	24.3	0.6
Gender			
Female	54%	53.8%	0.9
Male	46%	46.2%	
Birth weight†	2178 ± 603 (658–3650)	2180 ± 590 (620–3460)	0.9
<2500 g†	188 (68.6%)	187 (70.3%)	0.7
<1500 g†	44 (16.1%)	38 (14.3%)	0.6
Birth height	43.4 ± 3.3 (29–50)	43.3 ± 3.9 (28–51)	0.9
Apgar score at 1. min*	9 (0–10)	9 (1–10)	0.6
Apgar score at 5. min*	10 (0–10)	10 (4–10)	0.9
Umbilical artery blood pH†	7.31 ± 0.06	7.30 ± 0.08	0.8
Umbilical artery blood base excess	–2.8	–3	0.5
Umbilical artery blood pH < 7.26†	29 (13.6%)	32 (13.2%)	0.9
Umbilical artery blood pH < 7.05†	1 (0.5%)	4 (1.6%)	0.4

\*Median (range).

†Number of patients (percent).

shown conflicting results. Some studies have shown no significant differences in multiple pregnancies and the general population [8,6,11,12]. In certain studies, a few specific parameters such as lower birth weights, discordance and cesarean sections were more likely in ART conceived multifetal gestations [8,12]. In contrast other studies showed significant differences in pregnancies conceived with ART [7,9,13].

In a review there were no significant difference in stillbirth, very low-birth weight infants, placenta previa, antepartum hemorrhage, preterm birth, PPRM, preeclampsia, perinatal mortality and congenital malformations. In this meta-analysis there was an increased risk of preterm birth and cesarean delivery rate among IVF twins [14].

In another meta-analysis, Helmerhorst *et al.* [15] reported significantly lower perinatal mortality for ART twins. This can be explained by the fact that monochorionic twins carry the highest risk of a poor outcome [16]. About 20% of all the twins are monochorionic, but the proportion is higher in spontaneous twins (30%) compared to ART twins (3.7–7%) [9,17,18]. This study represents our experience with multifetal gestations conceived by ART before the mandatory age-based single embryo transfer legislation in Turkey. We did not find significant differences for perinatal and maternal outcomes between ART and spontaneous conception multifetal pregnancies. In order to mimic clinical practice we did not exclude TTTS, multifetal reductions and triplets.



Table 4. Distribution of major fetal anomalies in multifetal gestations.

	ART multifetal gestations (n = 282)	Spontaneous multifetal gestations (n = 269)	p values
Congenital Anomalies*	20 (7.1%)	19 (7.0%)	NS
Cardiovascular*	8 (2.8%)	3 (1.1%)	NS
Face and Neck*	0	1 (0.4%)	NS
Genitourinary*	2 (0.7%)	1 (0.4%)	NS
Central Nervous System*	0	4 (1.5%)	0.04
Gastrointestinal*	4 (1.4%)	1 (0.4%)	NS
Chromosomal	1 (0.4%)	1 (0.4%)	NS
Metabolic	1 (0.4%)	0	NS
Others	3 (1.1%)	4 (1.5%)	NS
(Musculoskeletal, Multiple anomalies, skin and eyes)			
Developmental Growth Retardation	10 (3.7%)	5 (1.9%)	NS
Neurological Anomaly	1 (0.4%)	4 (1.5%)	NS

\*Number of patients (%).

As might be expected, ART population are on average older and are more frequently primiparous than the normal obstetric population. Age and nulliparity attributed risk factors for more serious perinatal and obstetric outcomes. To overcome the effect of age and nulliparity, each ART multifetal pregnancy was matched to one spontaneous multifetal pregnancy by age ( $\pm 3$ ) and parity in our study. Mean maternal age was  $31.4 \pm 4.8$  (18–41) in ART group and  $28.8 \pm 4.9$  in spontaneous group. There is inadequate data regarding whether or not multiples conceived by ART also have a higher chance for congenital malformations compared to those conceived spontaneously. In a study in 2001, 1093 twin pregnancies (consisted of dizygotic twins) analyzed by Lambalk and Hooft [9], found a non-significant, slightly higher rate of birth defects in the ART twins with a risk ratio of 1.54 which disappeared after correction for maternal age. In another study in which study population consisted of both dichorionic and monochorionic twins reported an incidence of birth defects even lower in twin infants conceived by ICSI than in those conceived naturally (odds ratio 0.86) [19]. This lower rate of malformations in ART twins may be attributed to the lower fraction of monochorionic twins in this group. Monochorionic twins have higher risk of congenital malformations [20].

Convincing reports including meta-analyses point to a higher relative risk of congenital malformations in children conceived after ART [21]. However, this is not a universal conclusion [22]. ICSI has been associated with a higher incidence of *de novo* sex chromosomal aberrations, inheritance of CF mutations and Y microdeletions, and spermatozoal aneuploidy [23]. We reported 7.1% congenital malformation in ART group. There was no difference in fetal malformation rates between ART and control group, but a higher rate of central nervous system malformation was observed (4 in control, 0 in ART group,  $p = 0.04$ ) in spontaneous group. Anomalies were neural tube defect, hydrocephaly and ventriculomegaly. These findings are consistent with previous data. Interestingly we found significantly higher CNS malformation in natural conception group. This can be explained by lack of prenatal consulting and folic acid prophylaxis in spontaneous conceptions. In our study population women in spontaneous multifetal pregnancy group declared that they had not received folic acid prophylaxis.

Therefore, antenatal folic acid replacement could be a reason for low CNS malformation in ART multifetal gestations. In contrast to our results Ben Ami et al. suggested that twin pregnancies conceived by ART constitute a high-risk group for anencephaly, due to possible synergistic effect of twinning and ART [24].

There are few studies that compared growth of IVF and NC twins. Earlier studies found no evidence for differences in growth measures between IVF and NC twins until 3 years [25]. During follow-up period (mean postnatal follow-up was 27.6 months) 10 (3.7%) children in ART and 5 (1.9%) in control group had a developmental deficit. We found no evidence for differences for growth development delay in height and weight between ART and matched spontaneous conception twins. Brandes et al. found no significant difference in mental developmental indexes between multiples from IVF and control group [25]. Data about the risks of acquiring cerebral palsy in multifetal pregnancies compared to singletons are limited and conflicting. Only two controlled studies on neurological sequel in ART twins have been published. Similar adjusted risks of cerebral palsy in IVF/ICSI versus control twins were provided in both studies, although the only predictive factors of cerebral palsy were male sex and prematurity or low-birth weight [26,27].

Multifetal reduction which is a reduction procedure performed because of an excess number of fetuses *in utero* to maximize the chances of a delivery of at least one healthy child. The major complication of multifetal reduction is pregnancy loss. The international registry analysis of 3515 patients undergoing fetal reduction quoted an overall pregnancy loss rate of 9.6% [28]. Take home baby rate reported as 95% for triplets undergoing fetal reduction and 92% for those who starts with quadruplets [29]. We had no pregnancy loss in 28 interventions, 3 were to quadruplets, in our series. This could be a result of our experienced and proficient perinatology specialists who have a large series of multifetal reduction. Fetal reduction decision depends on the couple's social backgrounds, ethics and underlying beliefs. There is limited data on long-term effects and its neurological outcomes after fetal reduction of triplets or higher order pregnancy to twins.

Gortds et al. [30] stated that introducing a new law for single embryo transfer has resulted in no difference in the

overall pregnancy rate before and after the introduction (36 versus 37%), while twin pregnancies, however, decreased from 19 to 3%. This data indicates that elective single embryo transfer significantly decreases the multifetal pregnancy rate without a reduction in the overall pregnancy rate.

Some of the major limitations of our study were relatively low numbers of participants and limited follow-up. Subgroup analysis was not done to examine IVF, ICSI, fresh embryos, frozen embryos and spontaneously conceived multifetal gestations. Another weak point was selection bias due to participants of the study who delivered in a tertiary care center because one would anticipate more complications with multiple gestations. A major strength was this study represents our experience with multifetal pregnancies conceived with ART in a cohort of homogenous women at a single tertiary care center with standard data sheets and standard antenatal protocols. Umbilical artery blood pH, congenital anomalies and long term outcomes were rarely analyzed in similar studies. The data included women who underwent multifetal fetal reduction (not selective fetal reduction) or with TTTS in both groups in order to interpret current clinical practice.

Both neonatal and maternal outcomes are comparable between ART and spontaneous multifetal gestations. Congenital fetal malformation rates between ART and spontaneous multifetal pregnancies were similar except central nervous system malformation that was more likely in spontaneously conceived ones. Obstetricians caring for pregnancies resulting from ART are called on to counsel patients about the risks and outcomes of multiple pregnancies. The information provided from larger series may have implications for decisions surrounding multifetal pregnancy reduction and single embryo transfer.

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## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper

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