

ORIGINAL ARTICLE

Comparison of outcomes of twins conceived spontaneously and by artificial reproductive therapy

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Abstract

Objective: To compare the outcomes of twin pregnancies conceived by artificial reproductive techniques (ART) with those of spontaneous conception.

Study design: In this multicenter prospective trial, comparisons were made between methods of conception in twin pregnancies, for maternal and perinatal outcomes.

Results: Of 1001 twin pairs, 763/1001 (72.7%) were spontaneously conceived and 238/1001 (23.3%) were conceived by ART. There were no significant differences between the two groups with respect to obstetric complications. There were 13 per 1000 (20/1504; 1%) perinatal deaths in the spontaneously conceived group and 6 per 1000 (3/466; 0.6%) in the ART group ($p = 0.8141$). We found no differences in gestational age at delivery (median 36.9 versus 37.0 weeks), birth weight (median 2520 g versus 2538 g), or in a composite measure of adverse perinatal outcome (17% versus 15%) between the groups.

Conclusion: There were no differences in the rate of adverse obstetric or perinatal outcomes between twins conceived naturally compared with twins conceived by assisted conception.

Keywords

Assisted reproduction, mode of conception, perinatal outcomes, spontaneous conception, twin pregnancy

History

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Introduction

Artificial reproductive technology (ART) is being increasingly used worldwide in the treatment of infertility. There is a 27% incidence of multiple pregnancy associated with in vitro fertilization (IVF) compared with only 1% among spontaneous pregnancies [1]. Multiple pregnancies are associated with significantly increased morbidity during pregnancy, labour and the perinatal period. It is not clear if assisted conception twin pregnancies are associated with an even higher rate of complications.

Some studies [2–4] have reported that the adverse obstetric outcomes and the increase in the rate of preterm delivery, which are observed more commonly among ART twins, are due to innate characteristics of the sub-fertile population. Other authors [5,6] have concluded that ART-assisted conception does not confer an increase in risk. These studies however compared only dichorionic twins. Furthermore, some studies have suggested that a lower-than-expected morbidity rate in ART-derived twins can be attributed to a lesser proportion of monochorionic pairs when compared to spontaneously-conceived twins [7].

The different criteria used in the various studies to determine the outcomes have resulted in controversy and lack of uniformity while counselling women who have conceived twin pregnancy by ART.

This study aimed to compare obstetric and perinatal outcomes in spontaneously conceived and ART-derived twins.

Materials and methods

The ESPRiT (Evaluation of Sonographic Predictors of Restricted Growth in Twins) study was a multicentre, prospective, observational study of 1028 twin pregnancies. Eight tertiary centres in Ireland took part in this study between May 2007 and October 2009.

Each participating site was approved by the institutional review board and all the participants gave their consent to participate. All live twin pregnancies between 11 and 22 completed weeks of gestation were included in this study. The exclusion criteria were monoamnicity, fetal anomaly or aneuploidy in either twin. Study participants were directly interviewed by the research sonographer with regard to demographic data, background medical and obstetric information, including mode of conception.

Serial ultrasonography was carried out and all data were contemporaneously transferred to an ultrasound software

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system (Viewpoint; MDI Viewpoint, Jacksonville, FL) and further uploaded onto a central consolidated database.

The maternal demographics, obstetric characteristics, delivery method, birth weight, perinatal morbidity and mortality data were compared according to the mode of conception. These were further analysed based on the type of ART and chorionicity.

The twins were classified as small for gestational age when their birth weight was <5th centile for gestational age. Birth weight discordance was defined as a difference in birth weight of >20% between both fetuses.

Admission to the neonatal intensive care unit (NICU) and adverse perinatal outcome were analysed according to the mode of conception. Adverse perinatal outcomes were defined according to criteria described in the primary ESPRiT analysis [8]. The results of a prespecified secondary analysis of this study are presented here.

Statistical analysis

Statistical analyses were performed with SAS software (version 9.1; SAS Institute Inc., Cary, NC). Chi-square test was used to compare categorical variables and Wilcoxon rank sum was used to analyse continuous variables. A probability value of <0.05 was considered statistically significant. The study had sufficient power (80%) to detect a $\pm 8\%$ difference in morbidity outcomes in ART conceptions compared to spontaneous conceptions. If a particular mode of conception group had very few numbers, this was excluded from the model analyses but nevertheless summarized.

Results

Of the 1028 twin pregnancies recruited for the ESPRiT study; 1001 completed the study.

Table 1 depicts the mode of conception of the 1001 twin pairs. Seventy-six percent ($n=763/1001$) of the twin pregnancies were conceived spontaneously while 24% ($n=238/1001$) were conceived artificially. IVF was the method of choice in 72% of assisted conceptions.

The maternal characteristics of the two groups are depicted in Table 2. As expected, patients in the assisted conception group were significantly older than those conceived spontaneously (mean age in years 35.4 versus 31.9; $p<0.0001$). Those who conceived spontaneously were twice as likely to be multiparous (58% versus 29%; $p<0.0001$) and were significantly more likely to be smokers (15% versus 4%; $p<0.0001$). The body mass index of the spontaneously conceived women was higher than their ART counterparts ($p=0.04$).

Table 1. Method of twin conception.

Mode of conception	Number ($n=1001$)
Spontaneous conception	763 (76.2%)
Assisted conception	
Intrauterine insemination	2 (0.2%)
ICSI	23 (2.3%)
Ovulation induction	41 (4.1%)
IVF	172 (17.2%)

ICSI, intracytoplasmic sperm injection; IVF, invitro fertilization.

There were 800 dichorionic pregnancies. Seventy-one percent ($n=568$) of these were spontaneously conceived and 29% ($n=232$) were conceived by ART. Ninety-seven percent ($n=195$) of the 201 monochorionic twin pregnancies were spontaneously conceived.

As shown in Table 3, there was no statistically significant difference in the incidence of obstetric complications such as gestational hypertension/preeclampsia, gestational diabetes, preterm prelabour rupture of membranes, or preterm delivery.

Though there was an increased incidence of unclassified antepartum hemorrhage and placenta previa among women who conceived by ART, the rate of placental abruption was similar between the groups.

In our study population, 971 twin pregnancies reached potential viability (>24 weeks or 500 g birth weight) and mode of delivery was recorded for all participants. The overall caesarean delivery rate in our study was 620/971 (64%). The caesarean delivery rate was 175/231 (76%) in the assisted conception group in contrast to 445/740 (60%) in the

Table 2. Maternal characteristics by method of conception.

Maternal characteristic	Spontaneous conception $n=763$ (%)	Assisted conception $n=238$ (%)	p Value ^a
Maternal age (mean & SD) years	31.9 (5.4)	35.4 (4.1)	<0.0001
Parity (≥ 1 birth)	437 (58%)	68 (29%)	<0.0001
Caucasian	629 (92%)	187 (95%)	0.1257
Mean gestational age (wks) at recruitment	16	15	0.0221
Smoker	107 (15%)	9 (4%)	<0.0001
Previous caesarean	72 (9%)	18 (8%)	0.3777
Chronic hypertension	11 (2%)	1 (<1%)	0.2062
Pregestational diabetes	8 (1%)	1 (<1%)	0.3700
Maternal body mass index (kg/m^2)(mean and SD)	25.6 (4.9)	24.9 (4.1)	0.0687

SD, standard deviation.

^aThe χ^2 test was used to determine associations between maternal characteristics and mode of conception and Wilcoxon rank sum was used to analyse continuous variables.

Table 3. Obstetric characteristics by method of conception.

Obstetric characteristic	Spontaneous conception $n=763$ (%)	Assisted conception $n=238$ (%)	p Value ^a
Chorionicity			
Monochorionic	195 (26%)	6 (3%)	<0.0001
Dichorionic	568 (74%)	232 (97%)	
Gestational hypertension/ Preeclampsia	67 (9%)	25 (11%)	0.4218
Gestational diabetes	11 (1.4%)	6 (3%)	0.2605
PPROM	20 (3%)	5 (2%)	0.5812
Twin-twin transfusion syndrome	20 (3%)	NA	NA
Placental abruption	1 (<1%)	3 (1%)	0.0565
Antepartum haemorrhage (unclassified)	38 (5%)	24 (10%)	0.0043
Placenta previa	4 (<1%)	5 (2%)	0.0245
Obstetric cholestasis	7 (1%)	8 (3%)	0.0067
Pre-term delivery	133 (18%)	34 (15%)	0.4131

PPROM, preterm prelabour rupture of membranes.

^aThe χ^2 test was used to determine associations between obstetric characteristics and mode of conception. Wilcoxon rule sum was used to analyse continuous variables.

spontaneous conception group. This difference was statistically significant ($p < 0.0018$) (Figure 1).

The median gestation at delivery was 37 weeks in both ART and spontaneously conceived cohorts. There was no difference in birth weight according to mode of conception ($p = 0.5732$). Birth weight discordance and the proportion with severe discordance $>20\%$ were comparable among both twin cohorts.

Forty four percent each of the spontaneously conceived and ART twins were admitted to the NICU. The median neonatal length of stay was 8 and 7 days, respectively. There were 13 per 1000 (20/1504; 1%) perinatal deaths in the spontaneously conceived group and 6 per 1000 (3/466; 0.6%) in the ART group. This difference was not statistically significant ($p = 0.8141$).

A composite measure of adverse perinatal outcome (namely perinatal mortality, hypoxic ischaemic encephalopathy (HIE), periventricular leukomalacia (PVL), necrotising

encephalomyelitis (NEC), respiratory distress syndrome (RDS) or sepsis) did not differ significantly between the groups ($p = 0.4379$) even after adjustment for chorionicity, maternal age, parity, gestation at delivery and smoking status. These findings are summarised in Table 4.

Discussion

This large prospective multicenter study provides contemporary data demonstrating a lack of significant differences in the outcomes of twins conceived spontaneously or by ART.

In vitro fertilization 172/238 (72%) was the most common type of ART used. In our cohort, comparison between the various methods of ART (i.e. intrauterine insemination, ICSI, IVF, and ovulation induction) failed to demonstrate any differences in either maternal characteristics or obstetric outcomes. This study had sufficient power (80%) to detect a $\pm 8\%$ absolute difference in morbidity outcomes in ART

Figure 1. Mode of delivery of twins according to conception method.

* Total CS $p < 0.0018$; ** CS versus Labour $p = 0.0003$ (CS versus Labour).

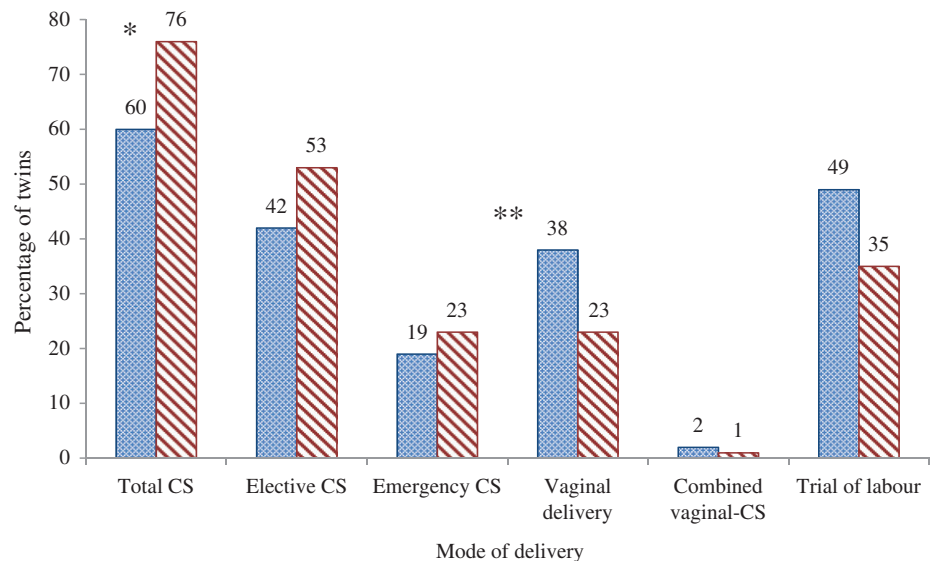


Table 4. Perinatal outcomes by method of conception.

Perinatal outcome†	Spontaneous conception $n = 1504$	Assisted conception $n = 466$	p Value adjusted*
Gestational age at delivery (median & IQR)	36.9 [35.0–37.7]	37.0 [35.3–37.9]	0.9466
Birthweight (g) (median & IQR)	2520 [2125–2850]	2538 [2160–2880]	0.5732
IUGR (<5th percentile)	90 (6%)	42 (9%)	0.0913
IUGR (<10th percentile)	181 (12%)	64 (14%)	0.6088
% Birthweight discordance ^a (median & IQR)	9% [5%–17%]	10% [4%–18%]	0.3031
>20% Birthweight discordance	162 (22%)	56 (24%)	0.8676
NICU admission	669 (44%)	203 (44%)	0.2069
NICU stay (days, median & IQR)	8 [1–21]	7 [0–18]	0.8883
Hypoxic ischaemic encephalopathy (HIE)	1 (0.1%)	1 (0.2%)	0.1045
Periventricular leukomalacia (PVL)	3 (0.2%)	3 (0.6%)	0.0925
Necrotising enterocolitis (NEC)	8 (1%)	3 (1%)	0.6240
Respiratory distress syndrome (RDS)	218 (14%)	61 (13%)	0.5707
Sepsis	95 (6%)	20 (4%)	0.6245
Perinatal death	20 (1%)	3 (0.6%)	0.8141
Composite outcome (death/HIE/PVL/NEC/RDS or sepsis)	261 (17%)	71 (15%)	0.4379

CS, caesarean section; IUGR, intrauterine growth restriction; HIE, hypoxic ischaemic encephalopathy; IVH, intraventricular haemorrhage; IQR, interquartile range; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.

^aBirthweight discordance is defined as the absolute difference in weight of the lighter twin taken relative to the heavier twin.

†Perinatal morbidity is based on all twins and excludes miscarriages ($n = 1970$).

*Adjusted for chorionicity, maternal age, smoker, parity and gestational age at delivery.

conceptions compared to spontaneous conceptions. True differences in morbidity of smaller magnitude were therefore not detectable based on our sample size of 1001 twin pairs.

Pregnancies conceived by ICSI were associated with a slightly higher rate of intrauterine growth restriction (IUGR) infants and birth weight discordance, as well as an increased incidence of NICU admission and length of stay. However, these parameters were not statistically significantly different when compared with other ART groups or twins conceived spontaneously. Pinborg's systematic literature review [9] also found that there were no differences in the obstetric and perinatal outcomes of ICSI and IVF twins.

The average maternal age at delivery is increasing internationally, and this is associated with an increasing use of ART [9–11]. In our study, as expected, we demonstrated that patients using ART were significantly older and of a lower parity than their counterparts who conceived spontaneously.

All the indices of adverse perinatal outcome were adjusted for chorionicity. This approach permitted inclusion of those cases of monochorionicity that arise from ART and that are subjected to the same potential for increased rates of obstetric intervention when compared to spontaneously conceived twins, while acknowledging that many perinatal twin complications are driven by chorionicity.

Seventy four percent of our spontaneously conceived twins were dichorionic while in the ART group the incidence of dichorionicity was 97%. Of the spontaneously conceived twins only 26% were monochorionic. This is in keeping with the fact that ART results in higher number of DC twins [9].

There was a comparable ($p = 0.4131$) preterm delivery rate of 18% and 15% in the spontaneous and ART groups, respectively. The median (and interquartile range) gestational age at delivery was 36.9 (35.0–37.7) and 37.0 (35.3–37.9) weeks, respectively. Only 1.5% of dichorionic twins in this study were delivered between 24 and 28 weeks. Many deliveries in that early preterm interval are iatrogenic, driven by severe fetal growth restriction or preeclampsia, rather than spontaneous labour. The absence of a significant difference between spontaneous and IVF pregnancies with respect to such determinants of many preterm births may serve to account for the comparable preterm delivery rates prior to 28 weeks. In Ireland, there is tendency toward a more conservative approach to elective preterm delivery and 68% of our dichorionic twins were delivered after 36 completed weeks of gestation.

However, various other studies [2,3,9,12] have demonstrated an increased preterm birth rate in the ART cohort. This is most likely attributable to an excess of elective late preterm births in uncomplicated twins in such studies. The Peristat data [13] demonstrated that Ireland had the lowest proportion of twins delivering prior to 37 weeks among participating countries.

A higher rate of preterm birth in the assisted conception population documented in other studies may be related to multiple factors [14] such as maternal stress, subclinical pelvic infection, micronutrient deficiencies and environmental exposures that are prevalent in the sub-fertile population. These factors and abnormal implantation due to suboptimal

endometrial function [15,16] in this group might also have accounted for a higher incidence of placenta previa ($p = 0.0245$) and unclassified antepartum hemorrhage ($p = 0.0043$) in the assisted conception group in our study.

Opinion is divided on whether ART confers an increased risk of adverse pregnancy outcome, with some studies advocating increased surveillance in ART pregnancies due to a heightened risk of perinatal mortality, preterm delivery and low birth weight [11,17]. In our study, perinatal mortality and serious neonatal morbidity (HIE, PVL, NEC, RDS or sepsis) did not differ significantly between the two groups. This observation lends support to the belief that an increased perinatal complication rate observed among ART pregnancies in other studies may be attributed to higher preterm delivery rates.

Other studies [18,19] have demonstrated comparable perinatal outcomes between the spontaneous and ART groups. Vasario et al. [6] and Yang et al. [5] stated that among dichorionic twin pregnancies where a fixed management protocol is applied, assisted conception is not associated with adverse perinatal or obstetric outcomes.

A retrospective cohort study [4] demonstrated a significantly increased perinatal mortality in spontaneously conceived twins when compared to ART twins. An increased proportion of monochorionic twins in the spontaneous conception group were shown to account for this observation. Sperling et al. [7] also reported a similar trend in a prospective multicenter trial. Ninety seven percent of monochorionic twins in our study were spontaneously conceived when compared with 71% of dichorionic twins. All analyses were adjusted for chorionicity.

There were 23 perinatal deaths in our study. Twenty (80%) of these occurred among spontaneously conceived twins and 3 (13%) were in the ART group. These differences were not statistically significant. Nevertheless, when the perinatal deaths were stratified according to chorionicity the spontaneously conceived monochorionic twins demonstrated a statistically significant ($p < 0.0001$) increase in perinatal mortality 18/195 (9.2 %) in comparison with other groups (dichorionic spontaneous conception (2/568; 0.4%) versus dichorionic ART (3/232; 1.3%), such that it is likely that an observed increase in mortality or morbidity observed in spontaneously conceived twins can be attributed to a higher rate of monochorionicity in this group.

Moreover patients who availed of assisted conception were more likely to have elective or emergency caesarean delivery without labour. Maternal and obstetrician's choice may account for this observation [3,19–21]. A systematic review and meta-analysis conducted by McDonald et al. [18] showed an increased rate of caesarean delivery among in vitro fertilization twins (odds ratio, 1.33; 95% CI, 1.06–1.67). Sullivan et al. [22] in their population-based study after IVF found that caesarean rates for assisted reproductive technology twins (62.0% versus 75.7%, OR: 1.92 [95% CI: 1.74–2.11]) were much higher than for spontaneously conceived twins. A 4-year survey of twins in Iceland and Scotland [17] showed that elective CD was used more often in the assisted conception group (odds ratio 2.57; $p = 0.003$). A CD rate of up to 90% in assisted conception twins has been quoted in the literature [3].

Trial of labour was twice as likely to be considered in women who conceived spontaneously (49% versus 35%; $p < 0.0001$). In fact a previous study [23] in the ESPRiT series had shown that the only characteristic that favoured a successful trial of vaginal delivery were multiparity and spontaneous conception.

The strengths of this study are that it is a contemporaneous prospective collection of data from a large population of twins. There was no selection bias, 100% delivery outcome was recorded and chorionicity was accurately determined prospectively. Small numbers of monozygotic twins in the ART group was a drawback that limited the interpretation of outcomes in this group.

This study supports the assertion that in the setting of twin gestation, assisted reproductive therapy does not confer an increase in the risk of adverse perinatal outcome.

The findings of this study are informative to fertility specialists and obstetricians in counselling patients seeking ART with respect to the anticipated outcome of twin pregnancy.

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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 article.

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