Obstetric outcomes of IVF trichorionic triamniotic triplets which are spontaneously or electively reduced to twins

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Abstract

Purpose To assess the obstetric outcome of IVF triplets which are spontaneously or electively reduced to twins.

Methods Retrospective study of trichorionic triplets (TT) and dichorionic twins (DT) conceived with IVF.

Results Compared to TT without reduction, TT with spontaneous reduction (SR) (OR: 5.6, 95% CI: 1.6–19.9) or elective reduction (ER) (OR: 14.0, 95% CI: 3.92–50.02) to twins were significantly more likely to be delivered at ≥ 34 weeks. Compared to DT likelihood of delivery ≥ 34 weeks was similar for SR and ER. Compared to TT without reduction, the risk of pregnancy loss before

24 weeks was not increased with SR or ER. Compared to DT the risk of pregnancy loss before 24 weeks was not significantly increased for SR or ER.

Conclusion Obstetric outcome of IVF triplets with SR is better than ongoing triplets and is similar to that of ER of TT and DT.

Keywords Assisted reproduction · Embryo reduction · IVF · Multiple pregnancy · Trichorionic triplet pregnancy · Fetal reduction · Dichorionic twins

Preliminary results of this study have been presented at the 66th Annual meeting of the American Society of Reproductive Medicine, Denver, Colorado (oral presentation) Fertility Sterility 2010;94(4, Supplement): S22

Capsule Obstetric outcome of IVF triplets spontaneously reduced to twins during the first trimester is similar to that of IVF triplets electively reduced to twins and dichorionic twins.

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Introduction

Pregnancy rates achieved with In Vitro Fertilization (IVF) currently exceed spontaneous conception rates in fertile couples [1, 2]. However, the current IVF success rates are achieved through the simultaneous transfer of several embryos, with the risk of multiple pregnancies. Women with multiple gestation are at risk of preterm delivery and associated complications which can result in infant death and handicap. Women with triplets or high order multiple pregnancies (HOMP) are given an option for elective embryo reduction (ER) in order to decrease these risks [3, 4]. The emotional burden of, and the ethical dilemmas associated with such a decision is stressful for the couple. Data regarding obstetric outcomes of triplets which have continued as triplets or been electively reduced to twins are available [5–7]. Couples are counselled using the available data to guide and help them for making decisions regarding their pregnancy. However, some women starting with triplets have spontaneous reduction of one of the embryos during the first trimester. Besides having the risks associated with triplets, having had a spontaneous reduction causes

further stress to these women. The situation brings uncertainty and there is limited data regarding prognosis of triplets which are spontaneously reduced to twins during the first trimester.

The present retrospective study aims to provide information about the obstetric outcomes of IVF triplet pregnancies which have been spontaneously reduced to twins during the first trimester, and compare them with triplets which were electively reduced to twins, triplets which continued as triplets beyond the first trimester, and dichorionic twins.

Materials and methods

The study population included all women who underwent IVF treatment at the McGill Reproductive Centre (MRC) between January 1997 and June 2009, the entire period of existence of the center, and conceived with triplets. Women with multiple pregnancies were identified using the MRC electronic database.

As per the institutional review board rules, approval from the institution's Director of Professional Services was acquired.

Only women who had complete obstetric follow up data available were included in the analyses (Fig. 1). Trichorionic triplet pregnancies were categorized as the following: (i) triplets which were spontaneously reduced to twins during the first trimester (spontaneous reduction group), (ii) triplets electively reduced to twins (elective reduction group), and (iii) triplets which continued as triplets (ongoing triplets). Triplet pregnancies which involved a monochorionic twin set or which were spontaneously reduced to singletons were excluded from comparative analyses. Women who conceived with dichorionic twins were selected as one of the control groups. Monochorionic twin pregnancies were excluded from the controls.

Procedures

Number of embryos with a heartbeat and chorionicity were determined by transvaginal ultrasound examinations performed between 6th and 8th gestational weeks. Chorionicity was also confirmed with post natal pathology examination of placentas where available. All women with multiple pregnancies were counselled regarding the risks associated and options available including ER. ER was done transabdominally by ultrasound

Fig. 1 Clinical pregnancies achieved at McGill Reproductive Centre during the study period and selection of the study population

guided intracardiac potassium chloride injection with a 20 – G needle between 12–14 weeks of gestation.

All women in the spontaneous reduction group (SR) had their pregnancies spontaneously reduced to twins between 6–14 weeks of gestation.

Outcome measures

Obstetric outcomes compared between groups were gestational age at delivery and the number of surviving infants.

Gestational age at delivery was categorized into five groups: <24 weeks (miscarriage), 24–27.9 weeks, 28–31.9 weeks, 32–33.9 weeks, and ≥ 34 weeks. The categories were arbitrarily determined according to clinical relevance. The highest quintile was chosen to be ≥ 34 weeks to reflect clinical practice as majority of clinicians would not attempt to prolong pregnancy after 34 weeks for triplets and would electively deliver at around 35th gestational week [5].

Statistical analysis

Chi-square with Yates correction, and Mann Whitney U tests were used for comparisons of categorical and continuous variables, respectively, between two groups. One way ANOVA or Kruskal Wallis tests were used for comparisons of continuous variables between >2 groups, depending on the distribution of the variables of interest.

Univariate logistic regression analyses were performed to evaluate the association of embryo reduction with the likelihood of delivery at ≥ 34 weeks. PASW Statistics 18, IBM Corp. Somers, NY was used for statistical analyses. All reported *p* values are two-sided and statistical significance level was set at 5%.

Results

There were 2300 clinical pregnancies (at least one embryo with a heart beat) within the study period. Seven hundred fourteen (31.04%) multiple pregnancies were identified. Among the 714 multiple pregnancies there were eight quadruplets and quintuplets (<1%), 110 triplets (15.4%), and 596 (83.5%) twins (Fig. 1). Triplets comprised 4.7% of all clinical pregnancies during the study period.

Eight triplets involving a monochorionic twin set, and three triplets which were spontaneously reduced to singletons within the first trimester were excluded from comparative analyses. Their results are presented separately. Complete follow up data were available for 81 (81.8%) of remaining 99 trichorionic triplets (TT). There were 483 (81.1%) twin pregnancies with complete follow up data.

Out of 81 women with TT, 26 women (32.1%) had ER to twins, 16 women (19.8%) had spontaneous reduction to

twins, and 39 women (48.2%) continued their pregnancies as triplets after 14th gestational week (Fig. 1).

Maternal age

Age $\pm$ standard deviation (SD) of the women at the time of conception were 34.3 ± 4.5 years in the triplet group, 34.2 ± 3.4 years in the SR group, 34.7 ± 4.0 in the ER group, and 33.9 ± 4.3 in the twin group (ANOVA, $p=0.83$).

Gestational age at delivery

Distribution of pregnancies across categories of time of delivery is shown in Fig. 2.

Likelihood of delivery at ≥ 34 weeks was 5.6 times (95% confidence interval 1.6–19.9, $p=0.008$) higher for women who had SR compared to women who did not have elective or spontaneous reduction of TT. Women who had SR had similar likelihood of delivery ≥ 34 weeks with women who conceived with dichorionic twins (OR: 2.069, 95% CI: 0.70–6.11, $p=0.19$). Likewise, women who had ER to twins were significantly more likely to deliver at ≥ 34 weeks (OR: 14.0, 95% CI: 3.92–50.02, $p<0.001$) compared to women who did not have any kind of reduction of TT. Compared to DTs, women with ER to twins were similarly likely to deliver at ≥ 34 weeks (OR: 1.21, 95% CI: 0.41–3.40, $p=0.73$). When women with SR and ER were compared the likelihood of delivery at ≥ 34 weeks was not different (OR: 2.5, 95% CI: 0.56–11.2, $p=0.23$).

Compared to women who continued triplet pregnancy beyond 14th gestational week without any kind of reduction, the likelihood of pregnancy loss before 24th gestational week was not increased for women who had either SR (OR: 0.29, 95% CI: 0.03–2.53, $p=0.26$, the number of pregnancy losses has been increased by one in the SR group for this analysis) or ER to twins (OR: 0.38, 95% CI: 0.07–2.0, $p=0.25$).

Fig. 2 Gestational age at delivery

Compared to DT pregnancies the risk of pregnancy loss before the 24th gestational week was not statistically significantly increased for women who had SR (OR: 3.29, 95% CI: 0.39–27.57, $p=0.27$, the number of pregnancy losses has been increased by one in the SR group for this analysis) or ER (OR: 4.39, 95% CI: 0.90–21.44, $p=0.07$). Results are summarized in Table 1.

Number of surviving infants

The numbers of surviving infants are presented in Table 2. Both infants survived in 14 (87.5%) and 23 (88.5%) pregnancies in SR and ER groups, respectively. There was only one survivor in two (12.5%) and one (4.0%) pregnancies in the SR and ER groups, respectively. None of the infants survived in two (7.7%) pregnancies in the ER groups. There was no statistically significant difference between the number of surviving infants in SR and ER groups (Chi-square, $p=0.87$).

The number of surviving infants was not different between the SR and DT groups (Chi-square, $p=0.92$).

At least one infant did not survive in 33.3% of triplet pregnancies.

Obstetric outcome of triplets which were spontaneously reduced to singleton

Three women aged between 33 and 38 years had spontaneous reduction to singleton. They all delivered at term, gestational age at delivery ranged between 38–40 weeks.

Obstetric outcome of triplets involving a monochorionic twin set

Complete data were available for 4 of 8 women. Women were aged between 29 to 36 years. One woman spontaneously lost the monochorionic twin set at 18th gestational week, and delivered the remaining singleton fetus at 29th gestational week. The baby was admitted to neonatal intensive care and subsequently discharged in good condition. Two women

spontaneously lost the singleton fetus during the second trimester and later delivered monochorionic twins at 30th and 37th gestational weeks. The remaining woman delivered triplets in 32nd gestational week. The singleton infant had acrocephalosyndactyly (Apert syndrome) and died on post natal 18th day.

Discussion

The results of the present study suggest obstetric outcomes of IVF triplets which spontaneously reduce to twins are similar to that of elective reduction to twins and pregnancies conceived as dichorionic twins. The study population included the vast majority of all eligible cases that occurred during a 12 year period in a busy IVF unit. Data were available for over 80% of all eligible trichorionic triplets which occurred in our unit. Presence of a systematic difference between women included in the study and those who were lost to follow up, i.e. the reason for loss to follow up being related to obstetric outcome, is unlikely. The vast majority of women lost to follow up were patients coming from out of our region and continued their obstetric follow up at their home towns. It has not been possible to contact these women despite reasonable effort.

Owing to the downward trend in the number of embryos transferred in IVF cycles, the incidence of IVF triplets is declining. During the period between 2004 and 2007, the incidence of IVF related triplets/HOMP has decreased from 4.9% to 3.7% of all IVF clinical pregnancies in the U.S., a relative decrease by 24.5% [8, 9]. However, the number of IVF cycles performed in the U.S. has increased from 127,977 to 142,435 during the same period [8, 9]. Resultantly, despite the decreasing rate of IVF triplets, the absolute number of women conceiving with triplets or HOMP following IVF is still substantial due to the overall increase in IVF cycles performed annually. Over 1300 women conceived with triplets or HOMP following IVF treatment in 2007 [9]. In the present study, 20% of women who conceived with triplets after IVF had spontaneous reduction to twins during the first trimester of pregnancy.

Table 1 Likelihood of pregnancy loss before 24th gestational weeks and delivery at ≥ 34 weeks' gestation after spontaneous or elective reduction of one fetus in trichorionic triplets conceived with IVF

	Spontaneous reduction ($n=16$)	Elective Reduction ($n=26$)
Pregnancy loss before 24th GW (Referrent: trichorionic triplets without any kind of reduction, $n=39$)	0.29 (0.03–2.53) ($p=0.26$)	0.38 (0.07–2.0) ($p=0.25$)
Pregnancy loss before 24th GW (Referrent: dichorionic twins, $n=483$)	3.29 (0.39–27.57) ($p=0.27$)	4.39 (0.90–21.44) ($p=0.07$)
Delivery ≥ 34 GW (Referrent: trichorionic triplets without any kind of reduction, $n=39$)	5.6 (1.6 to 19.9) ($p=0.008$)	14.0 (3.92–50.02) ($p<0.001$)
Delivery ≥ 34 GW (Referrent: dichorionic twins, $n=483$)	2.07 (0.70–6.11) ($p=0.19$)	1.21 (0.41–3.40) ($p=0.73$)

Results are presented as odds ratio and (95% confidence interval)

Table 2 The number of surviving infants

Number of survivors ^{a,b}	Spontaneous reduction (N=16)	ELECTIVE REDUCTION (N=26)	TWINS (N=463)	ONGOING TRIPLETS (N=39)
No survivor	0 (0)	2 (7.7)	10 (2.1)	9 (23.1)
One survivor	2 (12.5)	1 (3.9)	34 (7.0)	1 (2.6)
Two survivors	14 (87.5)	23 (88.5)	439 (90.9)	3 (7.7)
Three survivors	–	–	–	26 (66.7)

^a $p=0.87$ for spontaneous reduction versus elective reduction, ^b $p=0.92$ for spontaneous reduction versus twins

Compared to triplets managed expectantly, ER of trichorionic triplets to twins is reported to decrease the risk of early preterm birth between 24th to 32nd gestational weeks by two thirds [7]. However, the risk of miscarriage before 24th gestational week following embryo reduction has been a controversial issue. While an earlier study and meta-analysis reported that risk of miscarriage was increased approximately two fold after ER [7], a more recent review, taking into account operator's experience with the procedure and excluding series with ≤ 20 cases, reported similar risk of pregnancy loss before 24 weeks for reduced and non-reduced triplet pregnancies when the procedure was done by experienced teams [6]. Our findings are in accordance with the latter report. In a recent study, which is not included in either meta-analyses mentioned above, Skiadas et al. have reported pregnancy loss <24 weeks in 5.2% (10/191) of TT without reduction and 6.5% (6/92) with ER to twins ($p=0.66$) [5–7]. Available data on ER, in our opinion, do not support an increase in the risk of miscarriage <24 weeks when ER is performed by experienced operators.

It is suggested that the resorbing dead fetoplacental tissue rather than the ER procedure itself could cause increased risk of pregnancy loss before 24th gestational week following the procedure [7]. Our observations seem to support this opinion, as there was no statistically significant difference in gestational at age delivery between the SR and ER groups. While only women in the ER group have been subject to embryo reduction procedure, fetoplacental material was present in both groups, albeit a smaller amount in the SR group. However, despite the lack of a statistically significant difference, the presence of a trend towards higher miscarriage rate following ER can be mentioned in our study (rate of miscarriage 0% vs 7% in SR and ER groups, respectively).

Since DT and the SR group had similar obstetric outcomes, it appears that the mechanism causing the spontaneous loss of one embryo did not affect the growth of remaining embryos and pregnancy outcome. A uterine factor causing embryonic loss is unlikely to be present in this situation. The presence of a uterine factor could be expected to cause the loss of other remaining embryos as well, but the number of surviving

infants and other obstetric outcomes were similar between the SR group and dichorionic twins. The leading cause of embryonic loss during the first trimester is fetal aneuploidy, and it can be regarded the most likely etiological factor in this case [10]. Importantly, aneuploidy causing the loss of one embryo does not seem more likely to affect the remaining embryos. Women who experience spontaneous 3 to 2 reduction can be assured that their obstetric outcome will be better than ongoing triplets, and be similar to that of twins and elective reduction to twins.

It should be noted that the relatively small numbers of women in the ER and SR groups of the present study prevent definitive conclusions. To the best of our knowledge there is only one other case series reporting the obstetric outcome of IVF triplets which have been spontaneously reduced to twins [5]. Skiadas et al. recently reported the obstetric outcome of 26 IVF patients who conceived with trichorionic triplets and spontaneously reduced to twins before 12th gestational week [5]. They were compared with 81 women who underwent elective reduction to twins and 59 ongoing triplets. Similar to our results, Skiadas et al. reported that spontaneous reduction to twins occurred in 18% of IVF triplets, and spontaneous reduction extended time to delivery and significantly decreased the risk of delivery before 34th gestational week [5]. Our findings are consistent with those of Skiadas et al. and additionally demonstrate that the outcome of SR is similar to dichorionic twins. We also present the outcome of TT which involved a monochorionic twin set and TT which were spontaneously reduced to singletons.

In conclusion, IVF patients who conceived with TT do as well as dichorionic twins following SR or ER of triplets to twins. Importantly women with either SR or ER of TT to twins perform better than those who maintain a triplet pregnancy. Yet, it is prudent to limit the number of embryos transferred and avoid occurrence of triplets and HOMP in the first place.

Conflict of interest None.

References

1. Malizia BA, Hacker MR, Penzias AS. Cumulative live-birth rates after in vitro fertilization. *N Engl J Med*. 2009;360:236–43.
2. Engmann L, Maconochie N, Bekir JS, Jacobs HS, Tan SL. Cumulative probability of clinical pregnancy and live birth after a multiple cycle IVF package: a more realistic assessment of overall and age-specific success rates? *Br J Obstet Gynaecol*. 1999;106:165–70.
3. Dumez Y, Oury JF. Method for first trimester selective abortion in multiple pregnancy. *Contrib Gynecol Obstet*. 1986;15:50–3.
4. Evans MI, Fletcher JC, Zador IE, Newton BW, Quigg MH, Struyk CD. Selective first-trimester termination in octuplet and quadruplet pregnancies: clinical and ethical issues. *Obstet Gynecol*. 1988;71:289–96.
5. Skiadas CC, Missmer SA, Benson CB, Acker D, Racowsky C. Spontaneous reduction before 12 weeks' gestation and selective reduction similarly extend time to delivery in in vitro fertilization of trichorionic-triamniotic triplets. *Fertil Steril*. 2011;95:596–9.
6. Wimalasundera R. Selective reduction and termination of multiple pregnancies. *Semin Fetal Neonatal Med*. 2010;15:327–35.
7. Papageorgiou AT, Avgidou K, Bakoulas V, Sebire NJ, Nicolaides KH. Risks of miscarriage and early preterm birth in trichorionic triplet pregnancies with embryo reduction versus expectant management: new data and systematic review. *Hum Reprod*. 2006;21:1912–7.
8. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2004 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention 2006.
9. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2007 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention 2009.
10. Schmidt-Sarosi C, Schwartz LB, Lublin J, Kaplan-Grazi D, Sarosi P, Perle MA. Chromosomal analysis of early fetal losses in relation to transvaginal ultrasonographic detection of fetal heart motion after infertility. *Fertil Steril*. 1998;69:274–7.