

Comparison of Perinatal Outcomes of Singletons Following Vanishing Twin Phenomenon and Singletons with Initial Single Gestational Sac Conceived Following Assisted Reproductive Technology: A Retrospective Analysis

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ABSTRACT

Aim: The aim of the study was to compare the perinatal outcomes between singletons following vanishing twin phenomenon and singletons arising from initial single gestational sac following assisted reproductive technology (ART) treatment. **Setting and Design:** This was a retrospective cohort study. **Materials and Methods:** A retrospective cohort study included analysis of all singleton births following ART over a period of 7 years (January 2010 –December 2016). All women who underwent fresh or frozen embryo ART cycles were followed up. The study population included all singleton births following spontaneous reduction of one of the gestational sacs in dichorionic diamniotic twin pregnancies. The perinatal outcome of this group was compared with those of singletons arising from the initial single gestational sac. **Results:** A total of 521 singleton births were recorded during the study period. In the study group, 72 singleton births had spontaneous reduction of one of the gestational sacs (vanishing twin group) and the remaining 449 had an initial single gestational sac. The risk for low birth weight (LBW) (14/72, 19.4% vs. 96/449, 21.6%) and preterm birth (PTB) (17/72, 23.6% vs. 134/449, 29.8%) was not significantly different between those singletons who had spontaneous reduction from two gestational sacs to single sac compared to those with initial single sac. The miscarriage rate was significantly lower in vanishing twin group compared to control group (7/84, 8.3% vs. 157/622, 25.2%; $P = 0.01$). The subgroup analysis based on spontaneous reduction occurring before or after the appearance of the embryonic pole also showed similar risk of PTB (11/41, 26.8% vs. 9/31, 29.0%) and LBW (7/41, 17.1% vs. 9/31, 29.0%). **Conclusion:** Perinatal outcomes in singleton live births following vanishing twin phenomenon are similar to those pregnancies with an initial single gestational sac following ART.

KEYWORDS: Assisted reproductive technology, low birth weight, preterm birth, vanishing twin

INTRODUCTION

Assisted reproductive technology (ART) is the most advanced form of infertility treatment and more than 5 million babies have been born worldwide after introduction of the technology.^[1] Pregnancies following ART have been associated with adverse perinatal outcomes compared to natural conceptions.^[2] One of the main reasons for adverse perinatal outcomes following

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ART is multiple gestations. Twin gestations and higher order gestations are known to have adverse maternal and perinatal outcomes compared to singletons.^[2] However, even singletons conceived following ART were found to have higher incidence of low birth weight (LBW) and preterm birth (PTB) compared to singletons following spontaneous conceptions.^[2] The possible reasons for adverse perinatal outcomes in singletons following ART have been underlying infertility, *in vitro* gamete handling, and culture conditions.^[2]

Although elective single embryo transfer is being increasingly adopted in certain regions of the world, transfer of two or more embryos is still a common practice. The incidence of vanishing twin, that is, spontaneous reduction of the initial multiple-to-single gestational sac is between 10% and 30% following ART.^[3] The incidence of vanishing twin following ART is dependent on the number of embryos transferred. The incidence of vanishing twin is higher when the proportion of ART cycles with two or more embryos transferred is more. An earlier study found an incidence of vanishing twin to be 31% following ART.^[4]

There are conflicting studies regarding the obstetric and neonatal outcomes in survivors of vanishing twins following ART treatment when compared to singletons. Pinborg *et al.* found significantly higher risk of PTB and LBW in survivors of vanishing twin compared to singletons following ART.^[3] However, Chasen *et al.* found no difference in both LBW and PTB in the survivors of vanishing twins following ART.^[5]

In view of persisting ambiguity regarding perinatal outcomes, we planned a study to compare perinatal outcomes in survivor twin versus singleton following ART in our population.

MATERIALS AND METHODS

We conducted a retrospective cohort study and the study was planned in the Department of Reproductive Medicine of a university-level hospital from January 2010 to December 2016. All women who underwent fresh or frozen embryo ART cycles were included in the study.

We included women who conceived following fresh or frozen ART cycles and delivered a singleton. Those women who conceived and were found to have vanishing twin in the first-trimester ultrasound were included in the study group. Vanishing twin pregnancies were defined as dichorionic diamniotic (DCDA) gestation with a spontaneous reduction of one of the gestational sacs in the first trimester either before or after the appearance of an embryonic pole. For control, we included those

women who had initial single gestational sac in the first trimester.

We excluded those women who had a twin gestation which continued as DCDA or monochorionic gestation. We also excluded any higher-order pregnancies from our analysis. We planned a subgroup analysis within the vanishing twin group and divided it into two subgroups: Group A included women who had a spontaneous reduction before appearance of embryonic pole and Group B consisted of women who had a spontaneous reduction after the appearance of embryonic pole.

All women who had positive beta hCG underwent transvaginal ultrasound by an experienced clinician after 2 weeks. The following details were noted: location of pregnancy, viability, and number of gestation sacs.

In case twin pregnancies were identified, a diagnosis of DCDA or monochorionic diamniotic pregnancy was made by the presence of “lambda” sign (dichorionic) or “T” sign (monochorionic) during the first-trimester ultrasound. We screened the charts of all the women who underwent and conceived following ART, and an anonymized data collection was done. The pregnancies were followed up until delivery, and the couples were contacted for outcome-related details through E-mail and telephone.

The primary outcome was LBW defined as birth weight <2500 g. Other outcomes included PTB defined as delivery before 37 weeks, very low birth (defined as birth weight <1500 g), and live birth at term. Mode of delivery and miscarriage rate (defined as spontaneous or induced termination of pregnancy before 24 weeks of gestation) were also obtained.

Statistical methods

A sample of 264 participants (176 in singleton infants and 88 in vanishing twin) with the allocation ratio of 2:1 was required to obtain a difference of 14% in the LBW with 80% power and a 5% significance level. This 14% difference represented the difference between a 12% LBW rate in singleton infants group and a 26% rate in vanishing twin group (Shebl *et al.*). Collected data were entered into SPSS and data were analyzed using software, STATA, Version 13.1 (StataCorp, College Station, TX, USA). All the data were entered in SPSS and analysis was done using statistical software. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 1055 clinical pregnancies were recorded following fresh and frozen ART cycles during the study period, of which 622 (58.9%) were pregnancies with initial single gestational sac and 349 (33.1%)

constituted DCDA twin gestations. Further, 84 (24.1%) out of these 349 DCDA twin gestations underwent spontaneous reduction of one of the gestational sacs leading to vanishing twin. A total of 521 singleton births were recorded during the study period. No outcome data were available for 106 (10%) pregnancies and hence were excluded from the study. In the study group, 72 singleton births had spontaneous reduction of one of the gestational sacs (vanishing twin group) and the remaining 449 had initial single gestational sac. We also excluded the remaining 239 DCDA twin gestations which continued as twins from the study. The vanishing twin rate in the current study was (72/521, 13.8%). In the vanishing twin subgroup, 31 and 41 singleton births were recorded in Groups A and B, respectively [Figure 1].

The baseline characteristics in both the groups were similar except maternal age ≥ 35 years which was significantly higher in the control group (12/84, 14.3%) vs. 183/622, 29.4%; $P = 0.006$). No difference was noted in incidence of preexisting medical disorders such as hypertension and diabetes between the two groups [Table 1].

The risk for LBW was (14/72, 19.4% vs. 96/449, 21.6%) and PTB (17/72, 23.6% vs. 134/449, 29.8%) was not significantly different between those singletons who had spontaneous reduction from two gestational sacs to one sac compared to those with initial one sac [Table 2]. The live birth at term (≥ 37 weeks) (72/72, 100% vs. 446/449, 99.1%) and mean birth weight (2.8 vs. 2.27 kg) also was not significantly different [Table 2]. The miscarriage rate was significantly lower in vanishing twin group compared to control group (7/84, 8.3% vs. 157/622, 25.2%; $P = 0.01$) [Table 2]. The number of births by Cesarean section had similar distribution in both the survivors of vanishing twin and singleton groups (56/72, 77.7% vs. 331/449, 73.6%) [Table 2].

Table 1: Baseline characteristics of the groups

	Singletons after vanishing twin phenomenon (n=84) (%)	Singletons (n=622) (%)	P
Female age ≥ 35 years	12 (14.81)	183 (29.42)	0.006*
BMI ≥ 30 kg/m ²	10 (12.34)	81 (13.02)	0.86
Diabetes mellitus	20 (27.7)	159 (25.65)	0.87
Thyroid disorders	17 (20.98)	143 (23.0)	0.69
Hypertensive disorders	5 (6.2)	43 (6.9)	0.81
Fresh transfer	57 (70.4)	465 (74.71)	0.74
Frozen transfer	24 (29.7)	157 (25.24)	0.51

*Significant. BMI=Body mass index

Both subgroups A and B in the vanishing twin group were similar in all baseline clinical characteristics [Table 3]. The risk of PTB (11/41, 26.8% vs. 9/31, 29.0%) and LBW (7/41, 17.1% vs. 9/31, 29.0%) was similar in both groups as was the miscarriage rate 3/47 (6.3%) vs. 4/37 (10.8%) [Table 3].

DISCUSSION

The current study did not find any difference between the risk of PTB and LBW in singleton live birth following vanishing twin phenomenon compared to those with an initial single sac. The miscarriage rate was found to be significantly lower in vanishing twin arm compared to those with an initial single sac. The subgroup analysis within vanishing twin group did not reveal any difference in perinatal outcomes based on spontaneous reduction before and after appearance of the embryonic pole.

Chasen *et al.*, in their retrospective study, followed up ART pregnancies with spontaneous reduction ($n = 55$) documented before 14 weeks and compared it with a singleton ($n = 168$) and twin pregnancies ($n = 86$) which were also conceived following ART.^[5] When the spontaneous reduction group was compared to singleton group, the risk of PTB was not significantly different (12.7% vs. 8.9%; $P = 0.4$).^[5] In another retrospective cohort study by Pereira *et al.*, which compared perinatal outcomes between singletons ($n = 3196$) and survivors of vanishing twins ($n = 853$) following ART, found similar rates of PTB (5.86% vs. 7.04%) and very LBW (VLBW) (1.29% vs. 0.88%).^[6] The Cesarean section rates (47.9% vs. 46.2%) were also found to be similar in both the groups.^[6] La Sala *et al.* conducted a retrospective study ($n = 686$) which showed similar rates of PTB (16.7% vs. 15.9%)

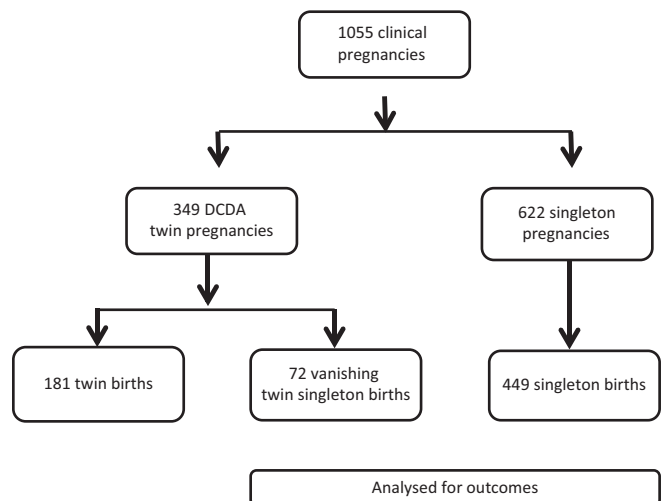


Figure 1: Algorithm for data analysis

Table 2: Perinatal outcomes of singletons following vanishing twin phenomenon versus singletons with initial single gestational sac

Outcomes	Singleton births in vanishing twin group (n=72)	Singleton births (n=449)	P
LBW (<2.5 kg)	14 (19.4)	96 (21.6)	0.67
PTB (<37 weeks)	17 (23.6)	134 (29.8)	0.30
Live birth at term (>37 weeks)	72 (100)	446 (99.1)	0.58
Mean birth weight (kg)	2.81 (0.57)*	2.78 (0.52)*	0.66
Delivery by caesarean section	56 (77.7)	331 (73.6)	0.70
Miscarriage rate	7/84 (8.3)#	157/622 (25.24)	0.01

*Standard deviation, #Calculated per clinical pregnancy.

PTB=Preterm birth, LBW=Low birth weight

Table 3: Baseline characteristics and outcomes based on the gestational age of vanishing twin phenomenon

	Before appearance of fetal pole (n=41) (%)	After appearance of fetal pole (n=31) (%)	P
Female age ≥ 35 years	5 (10.6)	7 (18.9)	0.82
BMI ≥ 30 kg/m ²	4 (8.5)	8 (21.6)	0.89
Diabetes mellitus	3 (6.3)	4 (10.8)	0.95
Thyroid disorders	7 (14.8)	8 (21.6)	0.13
PTB (<37 weeks)	11 (26.8)	9 (29.0)	0.41
LBW (<2.5 kg)	7 (17.1)	9 (29.0)	0.63
Miscarriage rate	3 (6.3)#	4 (10.8)#	0.82

#Calculated per clinical pregnancy. BMI=Body mass index,

PTB=Preterm birth, LBW=Low birth weight

and LBW (10.7% vs. 12.9%) between the spontaneous reduction group and the singleton group following ART.^[7] The findings of these studies are in agreement with the current study.

In a case-control study by Shebl *et al.*, comparing perinatal outcomes between survivors of vanishing twins ($n = 46$) and singletons ($n = 92$), demonstrated similar risk of PTB (19.6% vs. 8.7%) but significantly higher risk of LBW (26.1% vs. 12%; $P = 0.04$) and small for gestational age infants (32.6% vs. 16.3%; $P = 0.03$) in vanishing twin arm.^[8] The study population included monozygotic twin gestations which may have been a contributory reason for the contradictory findings in birth weight.

A study conducted by Pinborg *et al.* compared the maternal and neonatal outcomes of survivors of 642 vanishing twins with 5237 singletons with initial single gestation sac and 3678 twin pregnancies.^[3] The odds for increased risk of LBW singletons and VLBW singletons was 1.7 times and 2.1 times, respectively,

higher in the vanishing twin group when compared to singletons ($P < 0.001$).^[3] Similarly, the number of PTB (13.2% vs. 9%; $P = 0.001$) was also higher in the survivor group. The mean birth weight (3.2 vs. 3.4; $P = 0.001$) was also found to be significantly lower in the survivor group as compared to the singleton group.^[3] The findings of this study are in disagreement with the current study finding. In a study by Pinborg *et al.*, the inclusion of pregnancies with spontaneous reduction beyond the first trimester (up to the third trimester) could explain the contrary findings since the risk of adverse obstetric and perinatal outcomes increase with higher gestational duration.^[3]

Another population-based retrospective cohort study by Evron *et al.*, which included vanishing twins ($n = 278$) and singletons ($n = 252994$) showed a significantly higher risk of LBW (30.2% vs. 7.7%; $P = 0.001$) and VLBW (10.8% vs. 1.2%; $P = 0.001$) weight in vanishing twins.^[9] The study included pregnancies conceived spontaneously and following fertility treatment. The proportion of pregnancies conceived following fertility treatment was significantly different, 35% in the vanishing twin group and 2% in the singleton group which may have influenced the above findings.^[9]

The miscarriage rate was found to be significantly lower in the vanishing twin group. The possible reason could be significantly higher proportion of women with age ≥ 35 years in the singleton group which may have been a contributory factor for higher miscarriage in the same group.

No significant difference was found in the risk of LBW or PTB in vanishing twin subgroups depending on spontaneous reduction occurring before or after the appearance of fetal pole. Pinborg *et al.* found that the risk of adverse outcomes typically mean birth weight, PTB (11.35 vs. 9.1%; $P = 0.07$), and LBW (9.9% vs. 6.3%; $P = 0.001$) increased if the spontaneous reduction occurred after 8 weeks, which is contrary to our findings.^[3]

The small sample size and the retrospective nature of the study are some of the limitations of the current study. Due to the smaller sample size, type II error cannot be ruled out. Since we relied mainly on records for information regarding the patient, certain neonatal outcomes such as congenital anomalies and admission to intensive care units could not be assessed.

CONCLUSION

The present study suggests that perinatal outcomes in singleton live births following vanishing twin phenomenon are similar to those pregnancies with an

initial single gestational sac following ART. We may have to consider pooling the results of all the available studies to arrive at more definitive conclusions.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. McDonald SD, Murphy K, Beyene J, Ohlsson A. Perinatal outcomes of singleton pregnancies achieved by *in vitro* fertilization: A systematic review and meta-analysis. *J Obstet Gynaecol Can* 2005;27:449-59.
2. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: A systematic review and meta-analysis. *Hum Reprod Update* 2012;18:485-503.
3. Pinborg A, Lidegaard O, la Cour Freiesleben N, Andersen AN. Consequences of vanishing twins in IVF/ICSI pregnancies. *Hum Reprod* 2005;20:2821-9.
4. Pradhan S, Kamath MS, Selliah HY, Thomas S, Chandy A, Aleyamma TK. Comparison of perinatal outcomes of vanishing twin and twin pregnancies conceived following assisted reproductive technology: A retrospective analysis. *Middle East Fertil Soc J* 2016;21:253-8.
5. Chasen ST, Perni SC, Predanic M, Kalish RB, Chervenak FA. Does a “vanishing twin” affect first-trimester biochemistry in down syndrome risk assessment? *Am J Obstet Gynecol* 2006;195:236-9.
6. Pereira N, Pryor KP, Petrini AC, Lekovich JP, Stahl J, Elias RT, *et al.* Perinatal risks associated with early vanishing twin syndrome following transfer of cleavage- or blastocyst-stage embryos. *J Pregnancy* 2016;2016:1245210.
7. La Sala GB, Villani MT, Nicoli A, Gallinelli A, Nucera G, Blickstein I. Effect of the mode of assisted reproductive technology conception on obstetric outcomes for survivors of the vanishing twin syndrome. *Fertil Steril* 2006;86:247-9.
8. Shebl O, Ebner T, Sommergruber M, Sir A, Tews G. Birth weight is lower for survivors of the vanishing twin syndrome: A case-control study. *Fertil Steril* 2008;90:310-4.
9. Evron E, Sheiner E, Friger M, Sergienko R, Harlev A. Vanishing twin syndrome: Is it associated with adverse perinatal outcome? *Fertil Steril* 2015;103:1209-14.