Prevalences and pregnancy outcome of vanishing twin pregnancies achieved by in vitro fertilization versus natural conception

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Objective: To evaluate whether vanishing twin (VT) pregnancies achieved by in vitro fertilization and intracytoplasmic sperm injection (IVF–ICSI) had a more adverse perinatal outcome than those after natural conception.
Design: Longitudinal, retrospective cohort study.
Setting: Tertiary university hospital.
Patient(s): Three hundred and six (78 after IVF–ICSI and 228 after natural conception) VT pregnancies over a 22-year period, with VT cases matched to primarily singleton controls.
Intervention(s): None.
Main Outcome Measure(s): Obstetric and neonatal outcome data.
Result(s): The incidence of VT was statistically significantly higher after natural conception (18.2% of twins) than after IVF–ICSI (12.6% of twins). The odds of VT in pregnancies complicated with pregestational or gestational diabetes were disproportionally higher in IVF–ICSI cases than in spontaneously conceived VT pregnancies (adjusted odds ratio [AOR]: 0.80 vs. 3.10 and 1.00 vs. 1.07, respectively). Previous induced abortion (AOR 1.34) or second-trimester fetal loss (AOR 3.3) increased the risk of VT pregnancies after spontaneous conception. Gestational diabetes mellitus in both the previous (AOR 5.41) and the present (AOR 2.3) pregnancy as well as chronic maternal diseases (AOR 3.5) and placentation anomalies all represented independent risk factors for VT after IVF–ICSI.
Conclusion(s): Vanishing twin pregnancies had a lower prevalence and a worse perinatal outcome after IVF–ICSI as compared with those of their spontaneously conceived counterparts. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: IVF–ICSI, natural conception, perinatal outcome, singleton pregnancy, vanishing twin

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The increasing burden of infertility has led to an expanded rate of use of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (1), which has in turn enhanced twin conception rates and, presumably, the incidence of vanishing twin (VT) pregnancies (2). Double-embryo transfer is still routine in a number of countries (3) even though the benefit of a single-embryo transfer policy has already become evident (4). Some studies have reported that the obstetric outcome of the survivors of VT pregnancies after the IVF–ICSI technique is in between those of singletons and twins (5–9), whereas La Sala et al. (10) demonstrated that it is comparable to those of singletons.

The incidence of VT pregnancies varies between 10% and 39% in pregnancies resulting from IVF–ICSI (2,5,7,8,10–13), but the exact prevalence of VT after spontaneous conception has remained unclear (6, 14, 15). The etiology of the VT phenomenon is still obscure; however, placental degeneration (16) and chromosomal abnormality in the vanishing embryo (17) have been confirmed pathologically. Other possible causes, including inappropriate site for implantation, placental "crowding," intrauterine bleeding, and chronic maternal diseases have been proposed (6,18–21).

We hypothesized that there is a difference in perinatal outcomes between VT pregnancies after artificial conception and those after natural conception,

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possibly reflecting the potential differences between underlying pathomechanisms. We compared obstetric and neonatal outcomes between the survivors of VT pregnancies and matched singletons originating from single gestations after an IVF–ICSI procedure and after natural conception. Our purpose was to demonstrate the effect of the IVF–ICSI technique on the VT phenomenon and to determine the prevalence of VT pregnancies in iatrogenic and spontaneous twins.

MATERIALS AND METHODS

A retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, University of Szeged. The study included data abstracted from the medical database on VT pregnancies and matched controls between January 1, 1994, and November 30, 2014, that were subsequently delivered at our department. All IVF–ICSI treatments were performed at a single IVF center. In Hungary, sonographic confirmation of all pregnancies is obtained at 5 to 8 weeks with a repeat examination at 11 to 14 weeks to scan nuchal translucency systematically, thus providing a unique opportunity to identify all VT cases.

A total of 65,237 deliveries were singletons, 1,563 were twins, and 306 pregnancies were identified as VT syndrome cases, based on a review of all routine first-trimester scans, thus demonstrating a total rate of 4.69 out of 1,000 total pregnancies. Vanishing twin was diagnosed in cases where either [1] two viable embryos with cardiac activity with spontaneous reduction of one embryo or [2] a single viable embryo and an additional gestational sac were established before 14 weeks of gestation (14). A total of 78 VT cases resulting from 617 IVF with or without ICSI dichorionic twins (12.6%) and 228 VT cases were naturally conceived for 1,252 spontaneous dichorionic twin pregnancies (18.2%) (P=.002). We found that 36.8 VTs occurred out of 1,000 IVF–ICSI live births compared with a rate of 3.6/1,000 live births after natural conception (P<.001). All the women with VT pregnancies after IVF–ICSI underwent a double-embryo transfer procedure. All cases of single fetal loss at later gestation (>14 weeks) or pregnancies after ovulation induction/insemination were excluded from the analyses. Monochorionic twins (determined through the absence of a "twin peak" sign in sonography) and women undergoing iatrogenic reduction were also excluded.

For each case, three controls were matched according to the following criteria: singleton pregnancies started as singleton gestations achieved by natural conception or IVF–ICSI, which were equal in maternal age, previous gravidity, parity, and prepregnancy body mass index (BMI) and delivered after VT pregnancies in chronologic order. Demographic data, maternal characteristics, and obstetric and neonatal outcomes were retrieved from obstetric and neonatal databases and were exported to Microsoft Excel.

Vanishing twin cases were gathered from the sonography database at our department. Gestational age was established by the day of embryo transfer for the IVF–ICSI group and by sonographic measurement of the embryo in the first trimester for the spontaneous conception group. Intrauterine growth restriction (IUGR) was diagnosed when the growth curve had declined significantly below 10th percentile, resulting in a small fetus for pathological reasons. We defined birth weight as <2,500 grams for low birth weight and <1,500 grams for very low birth weight. Prematurity was defined as delivery at <37 weeks of gestation, and very premature birth was classified as birth at <32 weeks. The prepregnancy BMI registered at the initial visit during prenatal care was calculated as the body weight (kg) per height (m^2). Chronic maternal diseases (i.e., essential hypertension, cardiac, autoimmune and endocrine diseases, preexisting diabetes, and thromboembolic diseases) as risk factors for miscarriage were categorized into one variable to better interpret the statistical analyses. The demographic and obstetric history data and prevalence of chronic maternal diseases were analyzed. The following antepartum and intrapartum complications were examined: gestational diabetes mellitus (GDM), preeclampsia, placental abruption, placenta previa, retained placenta, and surgical delivery. Neonatal outcome measurements were as follows: gestational age, prematurity, birth weight, fetal growth disturbances (IUGR, very low birth weight, low birth weight), neonatal intensive care unit (NICU) admission, male sex, and congenital abnormalities.

All statistics were calculated using SPSS 22 (SPSS Inc.). The nonparametric design of the continuous variables was verified with the Shapiro-Wilk test. Vanishing twin was the major exposure variable. Univariate comparisons between VT pregnancies and controls both for IVF–ICSI and spontaneously conceived pregnancies were assessed with the Mann-Whitney U probe for continuous variables. Categorical variables were compared between the subgroups using chi-square tests, and odds ratios (OR) and Cornfield 95% confidence intervals (CIs) were also calculated. The resultant ORs for IVF and spontaneous pregnancies were compared with Mantel–Haenszel tests, providing an estimate of the effect of assisted reproductive techniques on the VT phenomenon. Multivariable logistic regression was performed to evaluate the factors determining VT pregnancies in both the IVF–ICSI and the spontaneous groups separately. Non-VT pregnancies were used as the reference group.

The multivariable dependence of the target variable on both categorical and continuous data were analyzed using logistic regression with stepwise (forward) model selection based on the likelihood ratio criterion (P_{in}=.05; P_{out}=.10). All the prepregnancy, maternal characteristics, and perinatal outcome variables represented independent factors. All the variables were adjusted for maternal age. Body mass index, parity, chronic maternal diseases, and obstetric history data, including miscarriage, termination of pregnancy, fetal loss in the second trimester, hypertensive disorder, prematurity, and IUGR in previous pregnancies constituted confounding risk factors.

The adjusted OR was also calculated with 95% CI. The two-tailed statistical significance level was set at 5%, and P values were adjusted using a Holm–Bonferroni correction for multiple comparisons (Mann-Whitney U tests and logistic regression analyses). The study was approved by the ethics committee of the University of Szeged, and the need for informed consent was waived.