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Analysis of pregnancy outcomes for survivors of the vanishing twin syndrome after in vitro fertilization and embryo transfer

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ABSTRACT

Objective: The purpose of this study was to compare pregnancy outcomes of in vitro fertilization (IVF) singletons diagnosed with vanishing twin syndrome with control pregnancies originating as singleton pregnancies and with twin pregnancies.

Study design: The current research included 206 survivors of a vanished co-twin, 1730 primary singletons and 662 primary twins. The study group was subdivided according to gestational age at the time of vanishing to give groups of early (≤12 weeks, group A) and late (>12 weeks, group B) survivors. Pregnancy outcomes were compared among study groups and controls.

Results: 10.54% of all IVF singleton deliveries originated from a twin gestation. Group A showed similar mean gestational age ($P = 0.148$) but higher proportion of preterm delivery ($P = 0.000$), extremely preterm delivery ($P = 0.000$), low birth weight ($P = 0.000$) and very low birth weight ($P = 0.000$) when compared with singleton controls. The comparison between group B and the singleton controls revealed dramatically higher frequency of preterm delivery ($P = 0.000$), extreme preterm delivery ($P = 0.000$), low birth weight ($P = 0.000$), very low birth weight ($P = 0.000$) and neonatal mortality ($P = 0.000$). When compared with twin controls, group A showed lower risk of adverse pregnancy outcomes; in contrast, group B still showed significant higher adverse risk.

Conclusions: IVF singletons with a vanished co-twin had a higher rate of adverse pregnancy outcomes in terms of preterm delivery and low birth weight, compared with IVF pregnancies that were originally singleton and twins, and the risk is increased with increasing gestational age at the time of vanishing.

Introduction

The vanishing twin (VT) syndrome, described as embryonic loss of one twin and survival of its co-twin, was documented more than two decades ago and has been a subject of interest in the literature since its description [1,2]. The term 'vanished twin' has been interpreted in many different ways ranging from first trimester missed abortion of one of the twins to vanishing of later gestational ages [3]. In its pure sense, the VT syndrome entails the spontaneous reduction of one fetus in a twin pregnancy during the first trimester [4].

The disappearance of gestational sacs or fetuses after documented fetal heart activity in multiple pregnancies is not unusual. However, there is scant information about the outcome of the singleton following the vanishing of its co-twin, and the etiology of this phenomenon also remains uncertain. Therefore, the consequences and the effect on the continuing pregnancy are subjected to debate and disagreement. Currently, the adverse obstetric and neonatal outcomes of this syndrome captured many researchers' attention and a multitude of adverse pregnancy outcomes were gradually described [5–7]. In order to account for fetal loss throughout the whole pregnancy, we decided to characterize 'vanished twin' as an empty sac or a first, second and third trimester intrauterine fetal demise.

Despite only a few studies have discussed the role of spontaneous reductions for the worse pregnancy outcomes of singleton pregnancies achieved after IVF with or without intracytoplasmic sperm injection (ICSI), researchers point out that VT syndrome is a possible cause of the increased morbidity in IVF/ICSI singletons [8].

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Currently, it has become evident that IVF/ICSI singletons are more likely to be born preterm [9] and to be of low birth weight than the naturally conceived counterparts [10]. Unfortunately, the evidence relating to the causes of these adverse outcomes in IVF singletons is less clear. Only a few studies based on clinical assisted reproductive technique pregnancies demonstrated that the frequency of singletons originating from a twin gestation is ranged from 10% to 30% [11]. Probably owing to the scarcely literature on this topic, the results are widely divergent. Previous reports have shown that the higher the number of gestational sacs the higher obstetric risks, irrespective of the final birth number [12,13]. Nevertheless, an Israeli study on 426 singleton IVF births reported no effect of the starting number of embryos on either gestational age or birth weight [14]. These different results may be attributed to their small sample size. A very recent study from the Danish population of births following IVF/ICSI pregnancies found more adverse outcomes among survivors of the vanishing twin that occur after 8 gestational weeks [15]. Consequently, investigators mentioned that such pregnancies need to be carefully monitored, and parents must be adequately informed about experiencing an early embryonic loss of one of their twins and the associated risks when transferring more than one embryo [16].

As the literature on the influence of spontaneous reduction in IVF/ICSI singletons is limited, the purpose of our present study was to evaluate incidence rates of vanishing twin in IVF/ICSI singletons, and to compare pregnancy outcomes, neonatal mortality and malformation rate in survivors of a vanishing co-twin with singletons from a single gestation and born twins.

Materials and methods

This retrospective analysis was conducted on the clinical data obtained from IVF/ICSI performed in International Peace MCH Hospital Shanghai Jiaotong University from Jan 2004 to April 2014, and was reviewed and approved by the Institutional Review Board Shanghai First People's Hospital. The key variables in each record of pregnancy were the date of embryo replacement and the personal identification number (PIN) code of the woman.

A total of 2598 deliveries were identified and extracted from a computerized data base. Of those, 1936 deliveries were singleton deliveries, which included 206 cases of vanishing twin. In our current research, the VT syndrome was defined in cases where two fetal pulses were demonstrated between 6 and 8 weeks and only one fetal pulse was demonstrated thereafter, and the cases were singled out as the study group. Pregnancies were followed by biweekly ultrasounds, the number and gestational age of fetuses lost was calculated at that time.

Only pregnancies that fulfilled the following inclusion criteria in gestational week 6–8 were eligible: (A) one fetus with positive fetal heart rate plus a gestational sac/fetus without fetal heart beat; (B) one viable fetus; or (C) two viable fetuses. Pregnancies in which more than two fetal hearts were beating, and gestations with no viable fetuses as well as monochorionic twins were excluded.

Subsequently, the study group was divided according to gestational age at onset of vanishing: early vanish (group A), co-twin perished $\leq$12 gestational weeks; and late vanish (group B), co-twin disappeared $\geq$12 gestational weeks. As a result, 138 cases belong to group A and 68 cases belong to group B. We compared the pregnancy outcomes of the remaining fetus in vanishing twin pregnancies with IVF/ICSI singleton pregnancies originating from a single gestation, and with IVF/ICSI twin pregnancies.

Gestational age was calculated according to the date of oocyte egg retrieval. Preterm delivery was defined as birth occurring before 37 weeks' gestational age, extremely preterm delivery as birth occurring before 32 weeks' gestational age [17]. Low birth weight was defined as birth weight under 2500 g, and very low birth weight as birth weight under 1500 g.

Data were compared among the groups in terms of maternal age, treatment cycles, duration of undesired childlessness, primary or secondary infertility, number of embryos transferred, mode of assisted reproduction (IVF or ICSI), gestational age, birth weight, neonatal malformation rate and neonatal mortality. Data are reported using the mean $\pm$ SD or n (%). The neonatal mortality rate was calculated by dividing the number of infant deaths by the total number of live births. The neonatal malformation rate was calculated by dividing the number of malformation infant by the total number of live births.

Statistics

The statistical analysis was carried out using the Statistics Package for Social Sciences (SPSS) software package (SPSS Inc., Chicago, IL, USA). Differences between parameters in the different patient groups were evaluated using the t-test where appropriate. Differences between proportions were evaluated using the Chi-squared test. A P-value of <0.05 was considered statistically significant.

Results

Vanishing twin proportion

During the current study period, there were 1936 singleton deliveries and 662 twin deliveries of pregnancies conceived by IVF/ICSI. Out of those singleton deliveries, 206 cases consisted the survivor cohort (group A and group B). Therefore, 10.54% of all IVF/ICSI singleton deliveries originated from a twin gestation. Among the 206 vanishing twin cases, 66.99% belongs to group A and 33.01% belongs to group B.

Characteristics and treatment data between group A and control groups

Baseline characteristics and treatment data between group A and control groups (include primary singleton and twin deliveries), such as mean maternal age, treatment cycle, duration of undesired childlessness, primary/secondary infertility, number of embryos transferred and ICSI rate are summarized in Table 1. Primary sterility was seen in approximately 53% of the patients in each group. No statistically significant differences were observed for maternal age, duration of undesired childlessness, and the frequency of primary sterility. Treatment cycle data in terms of previous IVF-embryo transfer cycles, the number of embryos transferred and the rate of ICSI for the study group A and control groups respectively were similar ($P > 0.05$).

Perinatal outcome data of the study group A and control groups

Gestational week, preterm delivery, extremely preterm delivery, birth weight, low birth weight, very low birth weight, neonatal mortality and malformation rate in group A and control groups were evaluated and listed in Table 2. The proportion of preterm delivery, extremely preterm delivery, low birth weight and very low birth weight were higher in group A when compared with singleton control group ($P = 0.000$). On the contrary, when compared with twin control group, group A had lower risk of preterm delivery ($P = 0.000$) and low birth weight ($P = 0.000$).