



Original article

Spontaneous abortion in multiple pregnancy: Focus on fetal pathology

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ABSTRACT

Multiple pregnancy with its wide array of medical consequences poses an important condition during pregnancy.

We performed perinatal autopsy in 49 cases of spontaneous abortion resulting from multiple pregnancies during the study period.

Twenty-seven of the 44 twin pregnancies ending in miscarriage were conceived naturally, whereas 17 were conceived through assisted reproductive techniques. Each of the 5 triplet pregnancies ending in miscarriage was conceived through assisted reproductive techniques. There was a positive history of miscarriage in 22.4% of the cases. Monochorionic placentation occurred more commonly in multiple pregnancies terminating with miscarriage than in multiple pregnancies without miscarriage. A fetal congenital malformation was found in 8 cases. Three of these cases were conceived through assisted reproductive techniques, and 5 were conceived naturally. Miscarriage was due to intrauterine infection in 36% of the cases.

Our study confirms that spontaneous abortion is more common in multiple than in singleton pregnancies. Monochorionic placentation predicted a higher fetal morbidity and mortality. In pregnancies where all fetuses were of male gender, miscarriage was more common than in pregnancies where all fetuses were female. Assisted reproductive techniques do not predispose to the development of fetal malformations.

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Introduction

Multiple pregnancy with its wide array of medical consequences poses an important condition during pregnancy. The significance of this is further increased by the recent spread of assisted reproductive techniques. In classic obstetric literature, the expected frequency of multiple pregnancy is calculated by the *Hellin formula* [6,8,18,23]. This formula predicts a ratio of 1 twin pregnancy in every 85 pregnancies, 1 triplet pregnancy in every 85² pregnancies, and 1 quadruplet pregnancy in every 85³ pregnancies. Nowadays, with the appearance of assisted reproductive techniques (ART), the incidence of twin pregnancies has increased two-fold, triplet pregnancies approximately twelve-fold and quadruplet pregnancies approximately eighty-fold compared to expected values by the *Hellin formula* [16]. Furthermore, it has been suggested by some researchers that gestational folic acid supplementation may also moderately increase the risk for multiple pregnancy at least in case of natural conception. However, subsequent papers failed to confirm this [19,27].

Based on what factors result in the development of multiple pregnancy, different kinds of placentation may occur [1,12,20,23,24]. In dizygotic fetuses, as well as in monozygotic fetuses when separation of amniotic sacks occurs within a few hours after fertilization of the egg, dichorionic diamniotic placentation develops. If the spatial separation occurs after separation of trophoblasts from embryoblasts, monoplacental diamniotic pregnancy will develop. Monochorionic monoamniotic pregnancy develops when the embryoblasts split immediately before or immediately after implantation.

The following maternal complications may be associated with multiple pregnancy: preeclampsia, anemia, cervical incompetence, abruptio placentae, and placenta previa. In terms of fetal complications with multiple pregnancy, increased perinatal morbidity and mortality and increased risk for miscarriage and premature delivery have been observed [5,18,20,23,24].

In this study, we attempted to evaluate and summarize the results of perinatal autopsies performed after spontaneous abortions that occurred in multiple pregnancies between gestational weeks 12–24. In cases of mid-term miscarriages in multiple pregnancy, perinatal autopsy may provide useful information relevant to the risk of future miscarriages. This may be especially valuable if fetal congenital malformation is diagnosed at the autopsy, providing a valuable tool in risk assessment for recurrence.

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Materials and methods

In this study, we report data from perinatal biopsies performed at The First Department of Gynecology and Obstetrics, Faculty of General Medicine, Semmelweis University, Budapest, Hungary after mid-term spontaneous abortions in multiple pregnancies during the study period of January 1, 1995–December 31st, 2010. We performed 49 perinatal autopsies from 44 twin pregnancies and 5 triplet pregnancies. Among the 17 multiple pregnancies conceived by ART, no case with the application of donor oocyte occurred. In each case, miscarriage occurred between gestational weeks 12–24. All ultrasound examinations were performed in our departmental ultrasound laboratory. Autopsies were performed in our departmental pathology laboratory based on protocols from our own department, as well as on those from other well-recognized pathology laboratories around the world [2,9,21,22,25]. During the autopsy, we were able to judge the type of placentation, the eventual presence of chorioamnionitis, as well as relevant characteristics of fetal pathology. The diagnostic criteria of chorioamnionitis were positive vaginal discharge sample taken during the pregnancy and histologically verified chorioamnionitis (the evaluation of vaginal discharge samples was performed in the departmental Chemistry Lab).

We have collected detailed information about the history concerning previous obstetrical complications (spontaneous abortion, missed abortion, premature birth, intrauterine death, ectopic pregnancy – *positive obstetric history*), and previous pregnancies with genetic malformations (*positive genetic history*).

If among the clinical diagnoses a likely obstetric etiology was found for the miscarriage, this was identified based on review of the medical records. If a malformation was present in previous pregnancies which was different from the condition giving rise to miscarriage in the current pregnancy, we regarded it as a nonspecific genetic risk. If, however, the malformation was identical in the present and previous pregnancies, risk was regarded specific for that condition. All relevant pieces of information were included in a computerized database. This database was then used for all subsequent analyses. For statistical significance, we used a *p* value of <0.05. Abbreviations used in this paper included: HC – hydrocephalus; SB – spina bifida; CAM – cystic adenomatoid malformation; TTTS – twin to twin transfusion syndrome.

Results

A total of 2141 autopsies were performed in our pathology laboratory during the study period. Out of these, 378 cases (17.6%) were perinatal autopsies due to miscarriage. During the study period of 16 years, the occurrence of spontaneous abortion was 0.91% per live birth, whereas the occurrence was higher in multiple pregnancies (7.3% per live birth). Out of the 378 miscarriage cases, miscarriage from multiple pregnancy was 49 (12.9%). Forty-four miscarriages out of the 49 (89.8%) were from twin pregnancies and 5 (10.2%) were from triplet pregnancies. Out of the 44 twin pregnancies, 27 (61.4%) were conceived naturally, while 17 (38.6%) were conceived through assisted reproductive techniques. All of the 5 triplet cases were conceived through assisted reproductive techniques. The total number of fetal samples amounted to 103.

A positive obstetric history was identified in 11 out of the 49 (22.4%) multiple pregnancy miscarriage cases. In 7 out of these 11 cases (63.6%), assisted reproduction techniques were used, while 4 (36.4%) were conceived naturally. The most common obstetric history was miscarriage in a previous pregnancy (5 cases).

The mean maternal age of patients undergoing ART was 33 ± 2.8 years vs. the mean median age value of pregnant women having

Table 1

Fetal gender distribution in twin pregnancies ending in spontaneous abortion.

Gender distribution	N	%
Male/male	23	52.3
Female/female	18	40.9
Male/female	3	6.8

a multiple pregnancy conceived spontaneously at 29 ± 3.2 years ($p < 0.05$).

The indication for applying ART technique was pelvic factor in 8/17 cases (47.1%), male factor in 5/17 cases (29.4%), ovulatory factor in 3/17 cases (17.6%), and unexplained infertility in 1/17 cases (5.9%).

Fetal gender distribution in the multiple pregnancies resulting in spontaneous abortion is displayed in Table 1. In our series, the number of cases where fetal gender was identical was significantly higher ($p < 0.05$) than the number of cases with heterogeneous fetal gender. In triplet pregnancies, male/male/male fetal gender distribution and female/female/female distribution were equally common (40%; 2 cases each). There was a single case with heterogeneous fetal gender (20%).

The type of placentation could be identified in 34 cases based on available information. These are described in Table 2. The ratio of monochorionic vs. dichorionic multiple pregnancies was 11:23. The difference in occurrence between mono- and dichorionic pregnancies was not significant ($p > 0.05$).

Given the small number of triplet pregnancies, maternal age was analyzed for the whole multiple pregnancy group, i.e., twin and triplet pregnancies taken together. In cases where no specific fetal pathology was identified on perinatal biopsy, the median maternal age was 30 ± 3.64 years (range: 16–45 years). In cases where a specific fetal pathology was seen, the maternal median age was 29 ± 5.46 years (range: 17–44 years). The difference between these two median values was not statistically significant ($p > 0.05$).

In terms of gestational age at the time of spontaneous abortion, there was no statistical difference between cases where a specific fetal pathology was found vs. cases where fetal pathology could not be identified. The respective values were 19.5 ± 2.77 gestational weeks in the positive fetal pathology group vs. 20 ± 2.35 gestational weeks in the group with no fetal pathology identified ($p > 0.05$). Fetal congenital malformation was identified in 8 out of the 44 twin pregnancy cases (18.2%); major malformations (which may explain the abortion) were verified in 6/44 (13.6%) and minor ones (not incompatible with postnatal life) in 2/44 (4.6%) cases. In the remaining 36 cases (81.8%), no specific fetal pathology could be identified. As is demonstrated in Table 3, a congenital malformation was present in both fetuses in 1 case, whereas in 7 cases, only one of the fetuses was affected (fetus A: the fetus closer to birth canal). In the cases where a congenital malformation could be identified, the pregnancy was naturally conceived in 63.5% of cases, while assisted reproduction techniques were used in 36.5% of cases. In the triplet pregnancy cases, a congenital malformation was identified in a single case. This congenital malformation was identified as *spina bifida lumbosacralis*. In this case, as in all other cases of triplet pregnancies, the pregnancy was conceived through assisted reproductive techniques.

Table 2

Types of placentation in multiple pregnancies ending in spontaneous abortion.

Placentation	N	%
Monochorionic–monoamniotic placentation	1	2.9
Monochorionic–diamniotic placentation	10	29.4
Dichorionic–diamniotic placentation	23	67.7

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