Evaluation and Management of Women who Have Experienced Stillbirth in Their Previous Pregnancies

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ABSTRACT

OBJECTIVE: To evaluate the subsequent pregnancy outcomes of women who have experienced unexplained stillbirth in their previous gestations.

STUDY DESIGN: This retrospective cohort consisted of 14 pregnancies who had stillbirth (without known risk factors) in their previous pregnancies. These patients had been included in a special preconceptional care program to be evaluated in terms of etiological risk factors for stillbirth. At least one of the risk factors, such as methylenetetrahydrofolate reductase polymorphisms, hereditary thrombophilias and autoimmune problems, were defined in this study population. After detection of pregnancy, the patients were administered low-dose low-molecular-weight heparin (enoxaparin, 1×2000 Anti-XA IU/0.2 mL/day), low-dose salicylic acid (100 mg/day) and low-dose corticosteroid (methylprednisolone, 1×4 mg/day orally) in necessary cases.

RESULTS: Out of 14 pregnancies, 4 (28.5%) ended up with miscarriages at 9, 11, 11 and 15 gestational weeks, respectively. The remaining 10 pregnancies ended up with alive deliveries. The mean gestational week at birth was 36.4±0.51, while the mean birthweight was 2882±381.01 g. Out of 10 pregnancies, only one was diagnosed as IUGR. Only two newborn necessitated hospitalization in the neonatal intensive care unit due to respiratory problems. Both newborns were discharged from the neonatal intensive care unit without any further complication at the post-partum 5th day.

CONCLUSION: Patients with a prior stillbirth should be screened for methylenetetrahydrofolate reductase polymorphisms, autoimmune problems and hereditary thrombophilias, especially in case of absence of any etiological factor. Management of these patients with low-dose aspirin, low-dose low molecular weight heparin and corticosteroids seemed to be beneficial for increasing live birth rates and avoiding obstetric complications.

Keywords: Autoimmunity, Hereditary thrombophilia, Methylenetetrahydrofolate reductase polymorphisms, Pregnancy, Stillbirth

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Introduction

Stillbirth is defined as fetal death prior to total expulsion of the fetus from the mother. The definition of stillbirth ranges from gestational weeks 16 to 28 and birthweights of 400g to 1000g (1). Despite these definitions, the most common cut-off values for gestational week and birthweight in the definition of stillbirth is 22 weeks and 500g (2). The overall stillbirth rate was found to be 15 per 1000 pregnancies, while it was 16.3 to 27.3 per 1000 deliveries in Turkey (3-5).

Stillbirth is a critical experience both for families and physicians since further pregnancies have 2.5 to 10 times higher risk of stillbirth (6,7). Furthermore, in subsequent pregnancies, there is also an increased risk of obstetric complications such as hypertension, diabetes or adverse neonatal outcomes (6).

The most important issue for the management of subsequent pregnancies is defining the etiologic factor for the stillbirth. Stillbirth is evaluated as a result of various maternal, fetal and placental disorders. The associated risk factors and

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etiological risk factors differ according to the income status of countries or gestational week (8). Knowing the cause of stillbirth is the key point for preventing any complication in subsequent pregnancies. Despite all research and efforts, 25-60% of stillbirths are nevertheless unexplained (9).

Thrombophilias have been associated with a 3.6 fold increase in rates of stillbirth (10). There is also a well-known relationship between autoimmunity and increased risk of stillbirth (11). Additionally, methylenetetrahydrofolate reductase (MTHFR) polymorphisms are linked to increased risk of fetal loss (12). Management of these patients with low-dose aspirin and enoxaparin was found to be beneficial for further pregnancies in some studies (13).

In this study, we evaluated the pregnancy outcome of patients with a history of stillbirth with a special treatment protocol.

Material and Method

We retrospectively evaluated the outcome of pregnancies with a history of stillbirth in their previous pregnancies. Stillbirth defined as an intrauterine fetal demise reaching 500 gr or 22nd gestational week. The required data was obtained from Hacettepe University, Division of Perinatology registries and the electronic database of our institutions between the years 2015-2018. Stillbirths due to known risk factors (chromosomal abnormality, congenital malformation, preeclampsia, diabetes mellitus, etc.) were excluded from our data. Finally, 14 patients had been investigated for various types of additional risk factors between their last two pregnancies. At least one of the following risk factors, such as MTHFR polymorphisms, additional hereditary thrombophilias and any autoimmune disease or autoantibody positivity, were described in all patients. A methionine restricted diet was applied for at least 3 months for patients with MTHFR polymorphism(s) and hyperhomocysteinemia. After detection of pregnancy, the patients were administered low-dose low-molecular-weight heparin (LMWH) (enoxaparin, 1×2000 Anti-XA IU/0.2 mL/day), low-dose salicylic acid (100 mg/day) and low-dose corticosteroid (methylprednisolone, 1×4 mg/day orally) in necessary cases. Low-dose corticosteroid was used for patients with autoimmune problems and complement system activation.

Any patients with at least one described risk factor were included in this study. The demographic information including obstetric history of the patients, maternal ages and gestational week of the stillbirth were recorded. Pregnancy outcomes including gestational week at birth or abortion, birthweight and admission to the neonatal intensive care unit (NICU) and any Apgar score ≤7 at the 1st, 5th or 10th minute were also recorded.

The acquired data were evaluated via descriptive statistics. All statistical calculations were performed with the Statistical Package for Social Sciences (SPSS) for Windows (SPSS version 23; SPSS Inc., Chicago, IL) statistical software package.

This retrospective study was approved by the Hacettepe University Ethics Committee.

***Table 1**: Patient characteristics, detected risk factors and gestational outcomes*

Patient	Age	Gravida	Parity	Living Child	Week of Stillbirth	MTHFR Polymorphisms	Hereditary Thrombophilias	Autoantibody or Autoimmune Disease	Pregnancy Outcome	Gestational Week	Birthweight	APGAR scores (≤ 7)	NICU
i	33	6	2	1	26	Normal	Normal	Sjogren Disease ANA Positivity	Delivery	36	2660	No	No
ii	42	5	2	1	26	Normal	Normal	ANA Positivity	Delivery	37	2270	Yes	Yes
iii	30	5	1	0	24	Normal	Factor V Leiden Heterozygous	Absent	Abortion	9			
iv	36	5	1	0	24	Compound Heterozygous	Normal	APA positivity	Abortion	10			
v	26	3	1	0	35	Compound Heterozygous	Factor V Leiden Heterozygous	Absent	Delivery	36	2800	No	No
vi	37	6	2	1	26	MTHFR 1298 Homozygous	Normal	ANA positivity	Delivery	36	3320	No	No
vii	34	6	2	1	32	MTHFR 677 Homozygous	Normal	ANA and APA positivity	Abortion	15			
viii	30	4	3	1	31	MTHFR 1298 Heterozygous	Normal	ANA positivity	Delivery	36	2380	No	No
ix	33	8	2	1	26	MTHFR 1298 Heterozygous	Normal	Absent	Delivery	36	3480	No	No
x	43	6	1	0	27	Normal	Normal	Hashimoto Disease ANA and APA positivity	Delivery	36	2940	Yes	Yes
xi	25	4	1	0	26	MTHFR 677 Homozygous	PAI Heterozygous	Absent	Delivery	37	3100	No	No
xii	34	6	2	0	26	MTHFR 677 Heterozygous	Normal	Anti-TPO positivity	Abortion	11			
xiii	29	2	1	0	25	MTHFR 677 Heterozygous	Normal	Absent	Delivery	37	2840	Yes	No
xiv	34	3	1	0	37	Compound Heterozygous	Normal	Absent	Delivery	37	3030	Yes	No

MTHFR: Methylenetetrahydrofolate reductase, NICU: Neonatal intensive care unit, ANA: Anti-nuclear antibody, APA: Anti-parietal cell antibody, PAI: Plasminogen activator inhibitor, TPO: Thyroid peroxidase

Results

This study consisted of 14 patients fulfilling all the study criteria. Demographic information of the patients, any existing additional risk factor and obstetric outcomes of the patients are summarized in table 1. The mean maternal age was 33.29±5.22. The mean gestational week of stillbirth at prior pregnancy was 27.93±4.12. Out of 14 pregnancies, 4 (28.5%) ended up with spontaneous abortions at the 9th, 11th, 11th and 15th gestational weeks, respectively. The remaining 10 pregnancies ended up with an alive fetus and no stillbirths occurred in this study group. The mean gestational week at birth was 36.4±0.51, while the mean birthweight was 2882±381.01 g. Out of 10 pregnancies, only one was diagnosed as IUGR. Four newborns had an Apgar score of seven or less at ten minutes, while only two of them necessitated hospitalization in the NICU. Indication for hospitalization was respiratory problems for both cases. Both newborns left the NICU on the 5th day.

Discussion

Management of patients with a history of stillbirth is challenging both for physicians and parents. Prognosis and management closely depend on the defined etiological factors. Patients with a stillbirth due to placental pathologies are more prone to placental complications in latter pregnancies (14). Managing patients with an unexplained stillbirth may be more challenging since there is no specific protocol determined for preventing further complications (15). On the other hand, physicians deliver patients earlier more often by cesarean section (16).

Thrombophilias or autoimmune disorders result in inflammatory processes at the maternal-fetal interface (injury of intervillous space structures, endothelial cells in spiral veins, syncytiotrophoblasts covering the chorionic villi, superficial and glandular epithelial cells in the decidua, endovascular trophoblasts etc.), which may cause impaired fetal perfusion and result in fetal death (17). Adverse outcomes were reported in autoimmune diseases such as Behcet disease, Celiac disease, inflammatory bowel diseases, Systemic lupus erythematosus (SLE) and Hashimoto's thyroiditis (18-21). MTHFR polymorphisms are also related to poor perinatal outcome and necessitate special antenatal care (12,22). These patients may constitute some part of the patients with unexplained stillbirths and defining risk factors may give physicians a chance to provide appropriate management in subsequent pregnancies. Low-dose aspirin and low-molecular-weight heparin have been found to increase live birth rates in patients with autoimmunity, thrombophilia and MTHFR polymorphisms (13,22,23).

In our series, 71.4% of the pregnancies ended up with a healthy newborn. This finding is important since the subsequent pregnancies of these patients are more likely to be complicated (24).

The limitations of this study were the relatively low number of cases and the retrospective design. Single center design and definition of a novel treatment approach are the strengths of this study.

In conclusion, patients with a prior stillbirth should be screened for MTHFR polymorphisms, autoimmunity and hereditary thrombophilias, especially in case of absence of any etiological factor. Management of these patients with low-dose aspirin, low-dose low-molecular-weight heparin and corticosteroids seem to be beneficial for increasing live birth rates and avoiding obstetric complications.

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