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CLINICAL ARTICLE

Etiology of spontaneous abortion before and after the demonstration of embryonic cardiac activity in women with recurrent spontaneous abortion

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ABSTRACT

Objective: To analyze the etiologic factors of spontaneous abortion in the first trimester among women with recurrent spontaneous abortion, specifically before and after the demonstration of embryonic cardiac activity. **Methods:** A retrospective analysis included women with recurrent spontaneous abortion admitted to a center in Guangzhou, China, for dilation and curettage after a spontaneous abortion in the first trimester between January 2008 and December 2012. The etiologic factors of spontaneous abortion occurring before versus after the demonstration of cardiac activity were compared. **Results:** A total of 232 women were included. Among 146 women with demonstrated cardiac activity before spontaneous abortion, 78 (53.4%) had an embryonic karyotype abnormality, 55 (37.7%) had traditional etiologic factors, and 34 (23.3%) had an unidentified cause. Among 86 women without cardiac activity, 41 (47.7%) had an embryonic karyotype abnormality, 28 (32.6%) had traditional etiologic factors, and 26 (30.2%) had an unidentified cause. After exclusion of abortions involving embryonic karyotype abnormalities, there was a higher incidence of APA positivity in the group with embryonic cardiac activity than in the other group (13/68 [19.1%] vs 1/45 [2.2%]; $P = 0.008$) and a lower incidence of subclinical hypothyroidism (8/68 [11.8%] vs 12/45 [26.7%]; $P = 0.042$). **Conclusion:** The distribution of etiologic factors in spontaneous abortion differs according to whether embryonic cardiac activity is recorded.

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1. Introduction

Recurrent spontaneous abortion (RSA) refers to the occurrence of more than two or three consecutive spontaneous abortions. Approximately 1%–3% of couples trying to conceive are affected, with 80% of the abortions occurring within the first 12 weeks of pregnancy [1,2]. The etiologic factors of RSA are genetic, endocrine, anatomical, and immune [3]. Many previous studies on the etiology of RSA lack an examination of the embryonic karyotype, but some studies [4,5] have found that more than half of all spontaneous abortions are associated with embryonic karyotype abnormalities. Therefore, etiologic studies that include an examination of the embryonic karyotype among women with RSA are of great importance.

Furthermore, evidence is mounting that the range of thyroid-stimulating hormone (TSH) levels that is considered to be normal should be lower during pregnancy than at other timepoints [6]. In 2011, the American Thyroid Association redefined the upper limit for a normal TSH value during pregnancy, decreasing it from 5.0 mIU/L to

2.5 mIU/L [7]. The rate of early abortion is significantly increased among women with an early-pregnancy TSH level in the range of 2.5–5.0 mIU/L (previously considered to be normal) [8]. However, in most previous studies of the etiology of RSA, TSH was measured before pregnancy. Few studies have investigated the incidence of subclinical hypothyroidism during early pregnancy among women with RSA since the normal range has been redefined.

Spontaneous abortion can occur at various stages of pregnancy depending on the underlying pathology [9]. For example, spontaneous abortions caused by fibroids tend to occur in mid-pregnancy [10]. Fetal aneuploidy is more likely to result in a pre-embryonic spontaneous abortion than in a loss occurring later in pregnancy [2]. Thrombophilias such as protein S deficiency are more likely to lead to fetal death than to a spontaneous abortion occurring earlier in pregnancy [11].

The presence of embryonic cardiac activity is the primary landmark of embryo development. The rate of spontaneous abortion decreases significantly after embryonic cardiac activity is demonstrated [12]. However, limited information is available on whether the etiology of spontaneous abortion occurring after the demonstration of cardiac activity is different from that of spontaneous abortion occurring before the presence of cardiac activity.

The aim of the present study was to analyze the etiologic factors of spontaneous abortion among women with RSA who underwent

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embryonic karyotype analysis and systematic etiologic examination including a thyroid function test during early pregnancy. In addition, the etiologic factors of spontaneous abortion occurring before versus after the demonstration of cardiac activity were compared.

2. Materials and methods

In a retrospective study, data were obtained for women with RSA who were admitted to Sun Yat-sen Memorial Hospital, Guangzhou, China, between January 1, 2008, and December 31, 2012. RSA was defined as two or more clinical pregnancies that ended in a loss during the first trimester. Included women had received dilation and curettage for a spontaneous abortion in the first trimester. Women were excluded if the systematic examination before or during pregnancy had not been completed, karyotyping of the chorionic villi was unsuccessful or had not been performed, or the spontaneous abortion occurred after more than 12 weeks of pregnancy. Women with a multiple, biochemical, or ectopic pregnancy were also excluded. All patients had provided written consent for tissue collection and the ethics review board at Sun Yat-sen Memorial Hospital, Sun Yat-sen University, approved the present study.

In accordance with the hospital protocol for women with RSA, the participants underwent systematic examination before and during early pregnancy. The following examinations were performed before pregnancy: hysteroscopy to evaluate the presence of uterine malformations (mainly septate, bicornuate, and unicornuate uterine abnormalities), intrauterine adhesions, polyps, and submucosal uterine fibroids; pelvic ultrasonography to evaluate the presence of a polycystic ovary; blood tests to evaluate the parental couple's chromosomes and the woman's levels of estradiol, follicle-stimulating hormone, luteinizing hormone, testosterone, prolactin, TSH, free thyroxine, free triiodothyronine, fasting plasma glucose (an oral glucose tolerance test was performed when necessary), and antiphospholipid antibodies (APAs) including anticardiolipin antibodies, anti- β 2 glycoprotein antibodies, and lupus anticoagulant factor. The following examinations were performed during early pregnancy: serial evaluation of human chorionic gonadotropin and progesterone levels, ultrasonography, and re-evaluation of the TSH, free triiodothyronine, and free thyroxine levels.

Polycystic ovary syndrome (PCOS) was diagnosed according to the Rotterdam criteria [13]. Subclinical hypothyroidism during the first trimester was diagnosed on the basis of a TSH level in the range of 2.5–10.0 mIU/L and normal levels of free triiodothyronine and free thyroxine [7]. APA positivity was defined by two or more positive APA results within a 12-week interval. Women classified as APA-positive were treated with low-molecular-weight heparin as soon as the pregnancy was demonstrated.

Transvaginal ultrasound examination was performed at 6–7 weeks of pregnancy. If no fetal cardiac activity was observed, the ultrasound examination was repeated after 1 week. If fetal cardiac activity was observed, the examination was repeated every 2 weeks until 10–12 weeks of pregnancy. Spontaneous abortion was diagnosed if the diameter of the gestational sac exceeded 20 mm and there was no yolk sac, the fetal crown–rump length exceeded 6 mm without cardiac activity, or there was a loss of previously identified cardiac activity. If there was doubt, the scan was repeated after 1 week. For the present study, the women were divided into two groups on the basis of whether embryonic cardiac activity had been observed before the diagnosis of spontaneous abortion.

After the diagnosis of spontaneous abortion, the product of conception was obtained by dilation and curettage under sterile conditions after obtaining the woman's informed consent. The chorionic villi were transported in Roswell Park Memorial Institute culture medium and subsequently separated from the maternal decidua and blood clots under a dissecting microscope. Karyotype analysis was performed with conventional tissue-culture and Giemsa-banding techniques.

The statistical analysis was performed with SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). Continuous data were reported as means and

standard deviations, and were analyzed with the *t* test. Categorical data were reported as percentages and were analyzed with the χ^2 test. $P < 0.05$ was considered statistically significant.

3. Results

A total of 146 women were included in the group for whom cardiac activity was recorded before diagnosis of spontaneous abortion, and 86 spontaneous abortions were included in the group with no cardiac activity. No significant differences in age, gravidity, number of spontaneous abortions, history of a live birth, or percentage of women at advanced age were observed between the two groups (Table 1). The pregnancy duration at spontaneous abortion in the group with cardiac activity was longer than that in the group without cardiac activity ($P < 0.001$).

In total, 113 (48.7%) of the 232 specimens had a normal karyotype and 119 (51.3%) had an abnormal karyotype. The frequency of an abnormal karyotype was not significantly different between the groups with and without cardiac activity (78 [53.4%] of 146 vs 41 [47.7%] of 86; $P > 0.05$). However, the range of karyotype abnormalities in the two groups did differ: the frequencies of viable autosomal trisomy, monosomy X, and triploidy were significantly higher in the group with cardiac activity than in the group without cardiac activity (Table 2). However, the frequency of double abnormalities was significantly lower in the group with cardiac activity than in the group without cardiac activity ($P = 0.002$).

Among the 232 women with RSA, 83 (35.8%) had abnormalities in etiologic factors other than abnormal karyotypes (henceforth, traditional etiologic factors), including 49 (21.1%) women with an abnormal endocrine factor (38 [16.4%] subclinical hypothyroidism; 5 [2.2%] PCOS; 8 [3.4%] diabetes mellitus; one woman had both PCOS and subclinical hypothyroidism, and another had both diabetes mellitus and subclinical hypothyroidism); 17 (7.3%) women with APAs; 16 (6.9%) women with a uterine abnormality (including nine women with a septate uterus and seven women with intrauterine adhesions); and 8 (3.4%) couples with a parental chromosomal abnormality (Fig. 1, Table 3). Among the 83 women who were affected by traditional etiologic factors, 30 (36.1%) also had an embryonic karyotype abnormality. Among the 149 women not affected by a traditional etiologic factor, 89 (59.7%) had an embryonic chromosomal abnormality. The cause of spontaneous abortion was unidentified in only 60 (25.9%) women (normal traditional etiologic factors and a normal embryonic karyotype). Additionally, all women had normal thyroid function before pregnancy.

In the group with demonstrated cardiac activity before the occurrence of abortion, 78 (53.4%) women had an embryonic karyotype abnormality, 55 (37.7%) had one or more traditional etiologic factors, and 34 (23.3%) had an unidentified cause. In the group without cardiac activity, 41 (47.7%) women had an embryonic karyotype abnormality, 28 (32.6%) had one or more traditional etiologic factors, and 26 (30.2%) had an unidentified cause. The prevalence of APA positivity in the group with cardiac activity was higher than that in the group without ($P = 0.025$) (Table 3). No differences between groups were found in the frequencies of other causes (Table 3).

In the group with cardiac activity before the occurrence of abortion, 21 (38.2%) of the 55 women with a traditional etiologic factor also had an embryonic karyotype abnormality. In the group without cardiac activity, 9 (32.1%) of 28 women with a traditional etiologic factor also had an embryonic karyotype abnormality. After the exclusion of women with an embryonic karyotype abnormality, the incidence of APA positivity in the group with cardiac activity was higher than that in the group without cardiac activity ($P = 0.008$), whereas the incidence of subclinical hypothyroidism was lower ($P = 0.042$) (Table 4).

4. Discussion

The present study comprised relatively comprehensive examinations and chorionic villus karyotype analyses among women with RSA,

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