Original Article

Epidemiological Survey and Risk Factor Analysis of Recurrent Spontaneous Miscarriages in Infertile Women at Large Infertility Centers

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Abstract

Background: A higher frequency of spontaneous miscarriage has been observed in infertile couples, and there is a higher prevalence of infertility among patients with a history of recurrent spontaneous miscarriages (RSMs; ≥2 miscarriages). This study aimed to determine the proportion of infertile patients with RSM and examine risk factors associated in patients with RSM being treated with assisted reproductive technologies.

Methods: This cross-sectional observational study was conducted at six reproductive medicine centers in three cities of China. Data of 751 patients with at least one spontaneous miscarriage were analyzed. Demographic data and etiological factors associated with infertility were compiled and compared between patients with a single spontaneous miscarriage (SSM) and those with RSM.

Results: Two hundred (26.6%, 95% confidence interval [*CI*]: 23.50–29.95%) patients experienced RSMs and 551 (73.4%) had a single miscarriage. The odds of RSM increased with increasing age (odds ratio [*OR*] = 1.06), uterine disorders (*OR* = 2.09), endocrine disorders (*OR* = 2.48), and immune disorders (*OR* = 2.98). Higher education level, masters or above, and a pelvic cavity disorder were associated with lower risk of RSM (*OR* = 0.27 and 0.46, respectively). Late spontaneous miscarriages were more frequent in patients with RSM than in those with a SSM (31.5% vs. 14.2%, respectively, $P < 0.001$) and were associated with a history of uterine cavity procedures (*OR* = 2.095) and cervical factors related to infertility (*OR* = 4.136, 95% *CI*: 1.012–16.90).

Conclusions: Compared to patients with only a SSM, the conditions of patients with RSM are more complicated. To increase the success rate of assisted reproductive technology, factors including uterus cavity adhesion, cervical relaxation, endocrine disorders, and immune disorders should be treated before assisted reproduction is initiated. These data may provide treatment guidance for infertile patients with a history of RSM.

Key words: Assisted Reproductive Technology; Epidemiological Survey; Infertility; Recurrent Spontaneous Miscarriage; Risk Factor

Introduction

Spontaneous miscarriage is a considerable issue in terms of its social and economic impact. Today, more and more women are delaying pregnancy until they are in their thirties or forties, and after the age of 30–35 years, the potential of fertility declines and the rate of spontaneous abortion increases.[1] There was a general consensus, based on historical data, that a diagnosis of recurrent spontaneous miscarriage (RSM) requires at least three consecutive miscarriages. However, the new social behavior of conception at an older age should cause this definition to be redefined

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because clinical investigation and possible treatments may be too late if initiated after the third miscarriage. In 2008, the American Society for Reproductive Medicine revised its definition of RSM as two or more failed pregnancies.[2]

An early study showed that, compared with the general population, a higher frequency of spontaneous miscarriage has been observed in infertile couples, and there is a higher prevalence of infertility among patients with a history of RSM.[3] Another study, however, reported that spontaneous abortion risk is not increased in pregnancies conceived with assisted reproductive technology (ART) as compared with spontaneously conceived pregnancies.[4] Infertility is defined by the American Society for Reproductive Medicine as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse.[2] Once infertile patients with a history of spontaneous miscarriages conceive with ARTs, the pregnancy outcomes or complications are closely related with the previous spontaneous abortion history.[1,3,5,6]

It has been demonstrated that the major etiological factors of female infertility include tubal and pelvic diseases, ovulation disorders, polycystic ovarian syndrome (PCOS), and premature ovarian failure.[7] In addition, patients with a history of spontaneous miscarriages may become infertile because of increased curettage of the uterus and advanced age, which have a negative effect on the endometrium, tubes, and embryo quality. In addition, patients with a history of RSM and those with only a single spontaneous miscarriage (SSM) commonly have multiple factors that can result in a miscarriage, and for patients with a history of spontaneous miscarriages attention is given to infertility treatment and pregnancy loss prevention, which complicates patient management.

As the relationships between infertility, ARTs, and RSM have not been clearly defined, the purpose of this study was to determine the proportion of infertile patients with a history of RSM and to examine etiological factors associated with RSM in these patients.

Methods

Ethical approval

This study was approved by the review boards of the respective reproductive medicine centers. All patients provided written informed consent for participation in the study and to have their medical data used for research purposes. All data were captured and handled in such a way so as to not reveal the identity of individual patients, and hence patient confidentiality was maintained at all times.

Site selection

This was a cross-sectional observational study conducted at reproductive medicine centers. Two reproductive centers in each city were stratified into general hospital affiliated (strata general) and maternity and child health-care hospital affiliated (strata special). Centers in the two strata performing more than 150 cycles of *in vitro* fertilization (IVF) per month were identified and approached as potential sites for this study. In three cities, nine reproductive centers in general hospitals and three centers in special hospitals were chosen as eligible for the study. One center in each stratum per city was then selected, and a total of six centers were invited to participate in the study. Ultimately, the study was conducted at a total of six reproductive centers in the cities of Beijing, Shanghai, and Guangzhou, China.

Patient inclusion criteria

Inclusion criteria for the study were female patients between 18 and 45 years of age (women of childbearing age) diagnosed with infertility and being seen at a reproductive medicine center. Patients were also required to have had at least one spontaneous miscarriage at ≤20 weeks' gestation irrespective of conception method (natural or ART) and to be willing to provide informed consent for participation in the study. Early spontaneous miscarriage was defined as <12 weeks' gestation and late spontaneous miscarriage was defined as between 12 and 20 weeks' gestation. Patients with a history of an induced abortion were excluded, as were patients with any reason in the opinion of the investigator that did not justify the patient's participation in the study.

Outcome measures

The primary outcome of the study was the proportion of infertile patients with RSM, defined as ≥2 spontaneous miscarriages at ≤20 weeks' gestation.[2,8] The percentages of patients with one, two, three, and four or more miscarriages were also calculated. Demographic and family data and etiological factors associated with infertility (ovulation disorders, uterine, cervical, tubal, and pelvic factors, endocrine disorders, immune disorders, reproductive tract infections, and chromosomal abnormalities) as diagnosed by the attending physicians were compiled and compared between patients with a SSM and those with RSM.

Statistical analysis

Evidence indicates that 32.5% of women who conceive with ARTs experience a miscarriage and 25.6% of patients have ≥2 spontaneous miscarriages.[6] A sample size of 675 patients produces a 2-sided 95% confidence interval (*CI*) with a precision equals to 0.033 ($d = 0.033$) if the estimated infertility rate is 25.6%. Considering 10% of patients may be excluded due to incomplete data, it was necessary to include 750 patients in the study.

Categorical data were expressed as number and percentage, and continuous data were expressed as mean and standard deviation. Univariate logistic regression was performed to examine risk factors (e.g., age, education level, and family history) of RSM. In a *post hoc* analysis, significant factors identified in the univariate analysis, and clinically important factors, were input into a multiple logistic regression model, and the final multiple logistic regression model was determined by a step-wise procedure. All the statistical analyses were 2-sided and performed with SAS 9.3 software (SAS Institute, Cary, NC, USA).

Results

Proportion of recurrent spontaneous miscarriage

A total of 757 patients were recruited, and six were excluded due to not meeting the inclusion criteria. Of the 751 eligible patients, 200 (26.6%, 95% *CI*: 23.50–29.95%) experienced RSMs and 551 (73.4%) had a SSM. Of the study population, 155 (20.6%) patients had two miscarriages, 34 (4.5%) had three miscarriages, and 11 (1.5%) had four or more miscarriages. The primary ARTs used were IVF or intrauterine insemination (IUI).

Recurrent spontaneous miscarriage and single spontaneous miscarriage

The baseline characteristics of patients with RSM and a SSM are summarized in Table 1. Patients with RSM were older (34.3 years vs. 32.8 years, respectively, $P < 0.001$) and more likely to have received a uterine cavity procedure (89.5% vs. 81.7%, respectively, $P = 0.011$) than those with a SSM. In addition, there was a smaller proportion of patients with a high school (16.5% vs. 24.0%, respectively) or master's (2.0% vs. 4.9%, respectively) degree in the RSM group as compared with the SSM group ($P = 0.036$).

A comparison of infertility-related factors between the two groups is shown in Table 2. Overall, fallopian tube factors (53.0%) were the most frequently reported in the study population, followed by ovulation disorders (23.4%), and pelvic cavity factors (10.9%). Univariate analysis revealed that patients with a uterine disorder (including endometrial polyps, intrauterine adhesions, uterine fibroids, uterine gland disease, endometritis, and uterine dysplasia) (13.0% vs. 6.4%, $P = 0.004$), endocrine disorder (including hypothyroidism and hyperthyroidism, and diabetes mellitus) (5.5% vs. 2.2%, $P = 0.024$), or immune disorder (including autoimmune diseases such as antiphospholipid syndrome and homologous immune diseases) (10.0% vs. 3.3%, $P < 0.001$) were more likely to have RSM. Of 11 patients with endocrine disorders, the most frequent disorders associated with RSM were hypo- (54.5%) and hyper-thyroidism (27.3%).

Results of the multivariable logistic regression analysis for factors associated with RSM are shown in Table 3. Six factors such as age, education, uterine factors, pelvic cavity factors, endocrine disorders, and immune disorders were included in the final model. The odds of RSM increased with increasing age (odds ratio [*OR*] = 1.06, 95% *CI*: 1.03–1.10, $P < 0.001$). Patients with a uterine disorder had one time increased risk of RSM than those without a uterine disorder (*OR* = 2.09, 95% *CI*: 1.18–3.68, $P = 0.011$). Patients with an endocrine disorder had a 1.5 times increased risk of RSM than those without an endocrine disorder (*OR* = 2.48, 95% *CI*: 1.02–6.05,

Table 1: Patient demographic, medical, and family data

Items	Recurrent spontaneous miscarriage ($n = 200$)	Single spontaneous miscarriage ($n = 551$)	*P*
Demographic			
Age (years)	34.3 ± 5.0	32.8 ± 4.8	<0.001*
Age of spouse (years)	35.9 ± 5.7	34.9 ± 5.7	0.032*
Menarche age (years)	13.8 ± 1.5	13.8 ± 1.6	0.787
Body mass index (kg/m^2)	22.9 ± 3.6	22.6 ± 3.3	0.341
Education			0.036*
Junior high school or below	64 (32.0)	155 (28.1)	
High school	33 (16.5)	132 (24.0)	
College or university	99 (49.5)	237 (43.0)	
Master or above	4 (2.0)	27 (4.9)	
Annual income (RMB)			0.426
<60,000	42 (21.0)	104 (18.9)	
60,000–199,000	108 (54.0)	320 (58.1)	
≥200,000	44 (22.0)	101 (18.3)	
Smoking	2 (1)	6 (1.1)	0.916
Alcohol consumption	1 (0.5)	8 (1.5)	0.312
ART numbers	85 (42.5)	225 (40.83)	0.682
Term pregnancy numbers	23 (11.5)	55 (9.98)	0.547
Surgery			
Uterine cavity procedure	179 (89.5)	450 (81.7)	0.011*
Pelvic procedure	75 (37.5)	201 (36.5)	0.797
Scarred uterus	12 (6.0)	18 (3.3)	0.096
Family history			
Recurrent spontaneous miscarriage in patient's sister or mother†	5 (2.5)	13 (2.4)	0.587
Infertility in patient's sister or mother†	3 (1.5)	9 (1.6)	0.959

1 USD = 6.4 RMB, 0.426. Data are presented as mean ± SD or *n* (%). *P* values were estimated by univariate logistic regression. *Statistical significance; †There were 32 missing data for annual income, 14 for family history of recurrent spontaneous miscarriage, and 3 for family history of infertility; ART: Assisted reproductive technology; SD: Standard deviation.

Table 2: Infertility-related factors in the recurrent and single spontaneous miscarriage groups

Items	Recurrent spontaneous miscarriage (n = 200)	Single spontaneous miscarriage (n = 551)	P
Ovulation disorder	38 (19.0)	138 (25.1)	0.085
Uterine factors	26 (13.0)	35 (6.4)	0.004*
Cervical factors	3 (1.5)	5 (0.9)	0.489
Fallopian tube factors	104 (52.0)	294 (53.4)	0.742
Pelvic cavity factors	15 (7.5)	67 (12.2)	0.073
Endocrine disorder	11 (5.5)	12 (2.2)	0.024*
Immune disorder	20 (10.0)	18 (3.3)	<0.001*
Reproductive tract infection	2 (1.0)	4 (0.7)	0.710
Chromosomal abnormalities	8 (4.0)	0	0.979
Male infertility	20 (10.0)	85 (15.4)	0.070
Unknown etiology	7 (3.5)	12 (2.2)	0.310

Data are presented as n (%). P values were estimated by univariate logistic regression. *Statistical significance.

Table 3: Multivariable logistic regression for factors associated with recurrent spontaneous miscarriage

Items	*OR* (95% *CI*)	*P*
Age	1.06 (1.03–1.10)	<0.001*
Education (Ref: Junior high school)	–	–
High school	0.61 (0.37–0.99)	0.047*
College or university	0.98 (0.67–1.44)	0.923
Master or above	0.27 (0.09–0.84)	0.023*
Uterine factor (Ref: No)	2.09 (1.18–3.68)	0.011*
Pelvic cavity factor (Ref: No)	0.46 (0.25–0.85)	0.014*
Endocrine disorder (Ref: No)	2.48 (1.02–6.05)	0.046*
Immune factor (Ref: No)	2.98 (1.48–6.02)	0.002*

*Statistical significance. –: Variable was not included in the final model; *OR*: Odds ratio; *CI*: Confidence interval; Ref: Reference group.

P = 0.046). Patients with an immune disorder had a two times increased risk of RSM than those without an immune disorder (*OR* = 2.98, 95% *CI*: 1.48–6.02, P = 0.002). A lower risk of RSM was found in patients with a high school degree (*OR* = 0.61, 95% *CI*: 0.37–0.99, P = 0.047) or master's degree (*OR* = 0.27, 95% *CI*: 0.09–0.84, P = 0.023) as compared to those with <9 years' education. In addition, patients with a pelvic cavity disorder had a lower risk of RSM than those without (*OR* = 0.46, 95% *CI*: 0.25–0.85, P = 0.014).

A total of 141 (18.8%) patients experienced at least one late spontaneous miscarriage and 601 (81.2%) had an early spontaneous miscarriage at <12 weeks' gestation. Late spontaneous miscarriages occurred more frequently in patients with RSM than in those with SSM (31.5% vs. 14.2%, respectively, P < 0.001).

Characteristics of patients with and without late spontaneous miscarriages

The description and comparison of the characteristics of patients with and without late spontaneous miscarriages is shown in Table 4. The average age was significantly higher in late spontaneous miscarriage patients compared with early spontaneous miscarriage patients (average age 34.7 vs. 33.6 years, respectively, P = 0.012). The average age of the spouse was also significantly higher in the late spontaneous miscarriage group compared with early spontaneous miscarriage group (average age of spouse 36.9 vs. 35.5 years, respectively, P = 0.021). With respect to surgical history, the frequency of uterine cavity procedures was significantly higher in late spontaneous miscarriage patients compared with early spontaneous miscarriage patients (91.49% vs. 81.97%, respectively, P = 0.006). With respect to etiological factors, the frequency of cervix factors was significantly higher in late spontaneous miscarriage patients compared with early spontaneous miscarriage patients (2.84% vs. 0.66%, respectively, P = 0.045). Multivariable analysis revealed that late spontaneous miscarriage was independently associated with a history of uterine cavity procedures (*OR* = 2.095, 95% *CI*: 1.112–3.949) and cervical factors (*OR* = 4.136, 95% *CI*: 1.012–16.90) [Table 5].

Discussion

The results of this study showed that RSM was associated with increasing age and that the odds of having RSM were increased in patients with uterine disorders, endocrine disorders, and immune disorders as compared to patients without these conditions. The smaller proportion of RSM patients with a pelvic cavity disorder suggests that there are other infertility factors (other than pelvic adhesions) in RSM patients, such as age and immune, endocrine, and genetic factors, and this is a unique finding of this study. Finally, the late spontaneous miscarriage rate was higher in the RSM group than in the SSM group (31.5% vs. 14.2%, respectively, P < 0.001) and was associated with a history of uterine cavity surgical procedures (*OR* = 2.095, 95% *CI*: 1.112–3.949) and cervical factors (*OR* = 4.136, 95% *CI*: 1.012–16.90).

RSM is a difficult problem for clinicians and patients, and it is estimated that, in approximately 50% of cases, a cause for RSM will not be identified.[9,10] Some authors have questioned whether there is a role for ART in patients with a history of RSM. Recently, Vissenberg and Goddijn[10] have suggested that there is not enough evidence to justify IVF or IUI for patients with RSM, and there is little

Table 4: Characteristics of late patients with and without late spontaneous miscarriages (n = 751)

Items	Late spontaneous miscarriage		P
	No (n = 610)	Yes (n = 141)	
Age (years)	33.60 ± 4.77	34.74 ± 5.13	0.012*
Age of spouse (years)	35.54 ± 5.49	36.89 ± 6.37	0.021*
Menarche age (years)	13.72 ± 1.52	13.91 ± 1.57	0.170
Body mass index (kg/m^2)	22.66 ± 3.32	22.89 ± 3.52	0.449
Surgical intervention history			
Uterine cavity procedure	500 (82.0)	129 (91.5)	0.006*
Pelvic procedure	225 (36.9)	51 (36.2)	0.874
Scarred uterus	23 (3.8)	7 (5.0)	0.514
Etiological factors			
Ovulation disorder	144 (23.6)	32 (22.7)	0.818
Uterine factors	44 (7.2)	17 (12.1)	0.058
Cervical factors	4 (0.7)	4 (2.8)	0.045*
Fallopian tube factors	329 (53.9)	69 (48.9)	0.284
Pelvic cavity factors	70 (11.5)	12 (8.5)	0.309
Endocrine disorders	19 (3.1)	4 (2.8)	0.999
Immune factors	28 (4.6)	10 (7.1)	0.222
Chromosomal abnormalities	5 (0.8)	3 (2.1)	0.176
Reproductive tract infections	5 (0.8)	1 (0.7)	0.999
Male infertility	80 (13.1)	25 (17.3)	0.177
Unknown etiology	15 (2.5)	4 (2.8)	0.768

Data were presented as mean ± SD for age, age of spouse, first marriage age, menarche age, and body mass index. Other data were expressed as n (%). *Statistical significance, P<0.05. SD: Standard deviation.

Table 5: Multivariable logistic regression for factors associated with late spontaneous miscarriage (n = 751)

Items	*OR* (95% *CI*)	*P*
Age	1.023 (0.971–1.078)	0.391
Age of spouse	1.023 (0.979–1.069)	0.315
Surgical intervention history		
Uterine cavity procedure (Ref: No)	2.095 (1.112–3.949)	0.022*
Etiological factors		
Cervix factors (Ref: No)	4.136 (1.012–16.90)	0.048*

*Statistical significance, P<0.05. *CI*: Confidence interval; *OR*: Odds ratio; Ref: Reference group.

evidence with regard to the usefulness of oocyte donation, preimplantation genetic diagnosis in carriers of a structural chromosome rearrangement, or for preimplantation genetic screening for unexplained RSM. However, Garrisi *et al*.[11] reported that preimplantation genetic diagnosis does improve pregnancy outcomes for women with idiopathic RSM, especially in patients with more than two losses and >35 years of age, and the improvement is not affected by fertility status.

It is estimated that 50–80% of first-trimester abortions have evidence of chromosomal abnormalities, and that the proportion of miscarriages due to chromosomal abnormalities decreases later in gestation.[1,12] Isolated early miscarriages are mostly due to chromosomal abnormalities, while in RSM, other nonembryonic factors such as luteal insufficiency or intrauterine factors lead to an abortion at a later stage of pregnancy.[5] This may explain our finding that the miscarriage rate after 12 weeks was higher in the RSM group than in the SSM group.

Poorolajal *et al*.[13] examined predictors of miscarriage in a matched case-controlled study that included 550 cases and 1091 controls. The *OR* of miscarriage was 1.58 for every 5-year increase in age, 0.20 for every live birth, and 3.43 for a history of previous spontaneous abortion. No significant associations were observed between miscarriage and body mass index, previous history of stillbirth, low birth weight, congenital anomalies, ectopic pregnancy, impaired thyroid function, or high blood pressure.

It has also been reported that chronic endometritis is associated with early pregnancy loss and/or fetal demise, and treatment with antibiotics increases the live birth rate.[14] Intrauterine bacterial infection has also been shown to be associated with early embryonic developmental arrest.[15] Our survey showed that the incidence of late spontaneous miscarriages was higher in cases of a RSM, and that late spontaneous miscarriage was associated not only with cervical factors, but also with uterine cavity procedures. Uterine cavity procedures mainly included curettage of the uterus because of a miscarriage, and can cause a thin endometrium, endometritis, and uterus cavity adhesion. Injury of uterine cavity could lead to placenta previa and premature rupture of membranes, which may result in a late spontaneous miscarriage.

This study found that the endocrine factors associated with RSM were primarily hyper- and hypo-thyroidism. It remains unclear if hyperthyroidism is associated

with infertility, but pregnant women with severe hyperthyroidism have been found to be at an increased risk of preeclampsia, preterm delivery, fetal growth restriction, thyroid storm, and congestive heart failure.[16] On the other hand, hypothyroidism is associated with early pregnancy loss and fetal problems including preterm birth, low birth rate, and abnormal neurocognitive development. However, a distinction must be made between overt hypothyroidism and subclinical hypothyroidism. Bernardi *et al*.[17] studied 286 women with a history of more than two pregnancy losses at <10 weeks' gestation and found that, although the prevalence of subclinical hypothyroidism was high, there was no statistically significant difference in the live birth rate between euthyroid women and those with subclinical hypothyroidism, or whether the hypothyroidism was treated or untreated. Testing thyroid function and thyroid-stimulating hormone during pregnancy for patients with subclinical hypothyroidism is regarded to be useful.

Farr *et al*.[18] analyzed data of 148,494 ART pregnancies conceived from 1999 to 2002 in the United States, and the Kaplan-Meier estimate of total risk of pregnancy loss was 29%, though ranged from 22% to 63% depending on patients' age and ART procedure. Approximately 58% of all pregnancy losses occurred by 6 weeks' gestation, and the conditional risk of pregnancy loss ranged from 10% to 45% at 6 weeks' gestation, from 2% to 7% in the first trimester, and was <2% after 20 weeks' gestation. Wang *et al*.[19] reported a positive correlation between body mass index and the risk of spontaneous abortion in women becoming pregnant with ART. On the other hand, Winter *et al*.[20] reported that smoking and transferring poor quality embryos increased the rate of early pregnancy loss, while age, obesity, PCOS, infertility etiology, and response to stimulation did not affect the rate of early pregnancy loss.

Interestingly, we found that patients with a high school degree or a master's degree had a lower risk of RSM than those with <9 years of education. We can only speculate regarding the reason for this finding, but believe it may be that patients with a less education may not have adequate knowledge of miscarriage and RSM and do not seek medical care when necessary.

There are some limitations to this study that should be considered. This study was a one-visit cross-sectional investigation at reproductive centers in three large Chinese cities, and a representative sample was collected from each center. Collecting all data from all six centers was beyond the scope of the study. The study was designed to collect a representative sample from all centers to reduce the cost and work required to do the analysis. Although the study was sufficiently powered, the design may have led to bias in site and/or patient selection. While independent risk factors for RSM were identified, the study design prevents the analysis of causality. Further studies are needed to clarify the relation between these risk factors and RSM in infertile females.

This study showed that RSM patients account for more than 25% of infertile patients with a spontaneous miscarriage history. Physicians should pay close attention to these RSM patients with possible risk factors such as older age, low education background, endocrine disorders, uterine factors, and immune disorders. Patients with a history of a uterine cavity procedure and cervical factors related to infertility are more likely to have late spontaneous miscarriages.

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Conflicts of interest

There are no conflicts of interest.

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