—Report on Experiments and Clinical Cases—

Clinical Characteristics of Pregnancies with a History of Recurrent Miscarriage at a Japanese Perinatal Center

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Objective: We examined obstetric and fetal/neonatal outcomes in women with a history of recurrent miscarriage.

Methods: We reviewed the obstetric records of all 5,829 nulliparous pregnant women who delivered at ≥14 weeks' gestation from 2008 through 2013 at our perinatal center. Of these women, 74 had a history of recurrent miscarriage (1.3%). The control population consisted of 4,176 nulliparous women without a history of miscarriage. Demographic information and characteristics of labor were extracted from patient charts.

Results: The rate of maternal age ≥40 years ($p<0.01$) and the rate of in vitro fertilization use ($p<0.01$) were higher in women with recurrent miscarriage than in women without miscarriage. Eleven women with recurrent miscarriage (14.9%) were treated with low-dose aspirin with and without subcutaneous heparin. In addition, the rate of cesarean delivery was higher in women with recurrent miscarriage than in women without miscarriage ($p=0.02$). However, fetal/neonatal outcomes did not differ significantly between the populations.

Conclusion: The pregnancy of women with a history of recurrent miscarriage is not associated with adverse outcomes at our perinatal center. (J Nippon Med Sch 2015; 82: 36–38)

Key words: perinatal outcome, pregnancy, recurrent miscarriage

Introduction

Miscarriage is the spontaneous pregnancy loss before the fetus has reached viability. Approximately 15% of clinically detected pregnancies result in miscarriage during the first trimester[1–3]. Although most miscarriages are sporadic and nonrecurrent[1], recurrent miscarriage, which is defined as the loss of 3 or more consecutive pregnancies[1–3], occurs in 0.5% to 3% of pregnant women. A history of (unexplained) recurrent miscarriage has been found to be associated with subsequent poor perinatal outcomes, such as perinatal loss, fetal growth restriction, preterm delivery, cesarean delivery, and hypertensive disorders[4–8]. In this study, therefore, we examined the obstetric, fetal, and neonatal outcomes in pregnant women with a history of recurrent miscarriage at our hospital.

Methods

We reviewed the obstetric records of all 5,829 nulliparous pregnant women who delivered at ≥14 weeks' gestation at the Japanese Red Cross Katsushika Maternity Hospital from 2008 through 2013. Of these women, 74 (1.3%) had a history of recurrent miscarriage (average number of miscarriages, 3.1±0.2; range, 3–4), which we defined as 3 or more spontaneous losses of pregnancy at <22 weeks' gestation. Of these 74 women, 5 (6.3%) had a history of 1 or 2 spontaneous miscarriages during the second trimester. The control population consisted of 4,176 nulliparous women without a history of miscarriage at <22 weeks' gestation. Demographic information and characteristics of labor were extracted from patient charts. Potential factors associated with adverse outcomes in pregnancies of women with a history of recurrent miscarriage were selected according to previous studies[4–8]: maternal age; parity; history of infertility, anticoagulant therapy; twin pregnancy; fetal demise; and obstetric complications, such as hypertension and hyperglycemia; gestational age

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Table 1 Obstetric characteristics and complications in nulliparous pregnant women with recurrent miscarriage and those without miscarriage who delivered at ≥14 weeks' gestation

	Without miscarriage (control)	With recurrent miscarriage	*P*-value
Number	4,176	74	
Maternal age			
<20 years	123 (2.9%)	0 (0%)	0.13
≥40 years	227 (5.4%)	15 (20.3%)	<0.01
In vitro fertilization use	339 (8.1%)	18 (24.3%)	<0.01
Anticoagulant therapy	0 (0%)	11 (14.9%)	<0.01
Twin pregnancy	178 (4.3%)	5 (6.8%)	0.29
Uterine myoma (≥3 cm)	446 (10.7%)	7 (9.5%)	0.87
Hypertensive disease	368 (8.8%)	8 (10.8%)	0.55
Hyperglycemia	82 (2.0%)	3 (4.1%)	0.20
Gestational age at delivery			
22–31 weeks	93 (2.2%)	2 (2.7%)	0.78
22–36 weeks	488 (11.7%)	9 (12.2%)	0.90
Cesarean delivery	1,097 (26.3%)	28 (37.8%)	0.03
Total blood loss ≥1,000 mL	466 (11.6%)	12 (16.2%)	0.17

Table 2 Fetal/neonatal outcomes in nulliparous pregnancies with recurrent miscarriage and those without miscarriage which delivered at ≥14 weeks' gestation

	Without miscarriage (control)	With recurrent miscarriage	*P*-value
Number	4,354	79	
Fetal demise			
at 14–21 weeks	6 (0.1%)	0 (0%)	0.74
at ≥22 weeks	4 (0.1%)	0 (0%)	0.79
Living fetus at delivery			
Number	4,344	79	
Apgar score at 1 min <7	114 (2.6%)	1 (1.3%)	0.45
Apgar score at 5 min <7	17 (0.4%)	0 (0%)	0.58
Umbilical artery pH <7.1	84 (1.9%)	0 (0%)	0.21
Trisomy 21	5 (0.1%)	0 (0%)	0.76

at delivery; mode of delivery; neonatal birth weight; Apgar scores at 1 and 5 minutes; umbilical artery pH at delivery; and neonatal hospitalization.

Data are presented as mean±SD or number (%). Cases and controls were compared by means of the x^2 test or Fisher's exact test for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Differences with $p<0.05$ were considered significant. If some significant adverse outcomes had been observed in the pregnancies with recurrent miscarriage, variables used in the multivariate model were those that had been shown on univariate analysis to have a significant ($p<0.05$) association with the outcomes in pregnancies with recurrent miscarriage.

Results

The rate of maternal age ≥40 years (crude OR, 4.42; 95% CI, 2.5–7.9; $p<0.01$) and the rate of in vitro fertilization use (crude OR, 3.64; 95% CI, 2.1–6.3; $p<0.01$) were higher in women with recurrent miscarriage than in women without miscarriage (**Table 1**). Eleven women with recurrent miscarriage (14.9%) were treated with low-dose aspirin (75–100 mg/day), with or without subcutaneous heparin, during their pregnancies ($p<0.01$ vs. control). Of these women, only 2 were defined as having thrombophilic disorders. In addition, the rate of cesarean delivery was higher in women with recurrent miscarriage than in women without miscarriage (crude OR, 1.71; 95% CI, 1.1–2.8; $p=0.02$). However, fetal and neonatal outcomes did not differ signficantly between women with recurrent miscarriage and those without (**Table 2**).

Discussion

In the present study, we found that women with recur-

rent miscarriage had different clinical characteristics and a higher rate of cesarean delivery than a control population who had deliveries during the study period; however there were no significant differences in the obstetric, fetal, or neonatal outcomes between the 2 populations, although these differences have been suggested to be associated with adverse outcomes in pregnancies[9,10].

Several previous studies have suggested mixed results for perinatal outcomes in women with a history of recurrent miscarriage[4–8]. Recently, Dempsey et al.[4] observed a reassuring prognosis for women with a history of unexplained recurrent miscarriage. They concluded that adverse events were prevented in these women by the earlier induced delivery because of a poor obstetrical history[4]. Therefore, adverse events in our patients with a history of recurrent miscarriage might have been prevented by the higher rate of cesarean delivery. In addition, anticoagulant therapy might also have contributed to the absence of significant differences in perinatal outcomes between the populations[1]. In the present study, only 2 of 11 women receiving anticoagulant therapy (18.2%) were considered to have had thrombophilic disorders. Antithrombotic treatment has not been generally been recommended for unexplained recurrent miscarriage; however, such treatment might benefit some patients, such as those with a heritable thrombophilia, with three or more pregnancy losses, or with a second-trimester loss; therefore, further trials of antithrombotic treatment are warranted[11].

In the present study, the pregnancies of women with a history of recurrent miscarriage were not associated with adverse outcomes at our Japanese perinatal center. However, a larger study without any bias may be helpful in confirming our current findings.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Rai R, Regan L: Recurrent miscarriage. Lancet 2006; 368: 601–611.
2. Takeshita T: Diagnosis and treatment of recurrent miscarriage associated with immunologic disorders: Is paternal lymphocyte immunization a relic of the past? J Nippon Med Sch 2004; 71: 308–313.
3. Takeshita T, Akira S, Araki T: Management of recurrent spontaneous abortion: the efficacy and the problem of immunotherapy (in Japanese). Nihon Ika Daigaku Zasshi 1998; 65: 421–424.
4. Dempsey MA, Flood K, Burke N, et al.: Perinatal outcomes of women with a prior history of unexplained recurrent miscarriage. J Matern Fetal Neonatal Med 2014; in press.
5. Jivraj S, Anstie B, Cheong YC, Fairlie FM, Laird SM, Li TC: Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study. Hum Reprod 2001; 16: 102–106.
6. Trogstad L, Magnus P, Moffett A, Stoltenberg C: The effect of recurrent miscarriage and infertility on the risk of pre-eclampsia. BJOG 2009; 116: 108–113.
7. Clifford K, Rai R, Regan L: Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod 1997; 12: 387–389.
8. Reginald PW, Beard RW, Chapple J, et al.: Outcome of pregnancies progressing beyond 28 weeks gestation in women with a history of recurrent miscarriage. Br J Obstet Gynaecol 1987; 94: 643–648.
9. Suzuki S, Miyake H: Obstetric outcomes of elderly primiparous singleton pregnancies conceived by in vitro fertilization compared with those conceived spontaneously. Reprod Med Biol 2007; 6: 219–222.
10. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ: Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Obstet Gynecol 2007; 109: 967–977.
11. Greer IA: Antithrombotic treatment for recurrent pregnancy loss? J Thromb Haemost 2011; 9 (Suppl 1): 302–305.

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