Recurrent miscarriage and risk of obstetric and perinatal complications in subsequent pregnancy: abridged secondary publication

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KEY MESSAGES

1. Chinese women with a history of recurrent miscarriage have an increased risk of several obstetric and perinatal complications in the subsequent pregnancy.
2. Women with a history of recurrent miscarriage should be offered specialist obstetric care from the start of pregnancy, with emphasis on strategies to manage the increased risk of preterm birth, small for gestational age, and perinatal death.

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Introduction

Miscarriage is estimated to occur in 11% to 20% of all clinically recognised pregnancies before the 24th week of gestation. The European Society of Human Reproduction and Embryology recommends to define recurrent miscarriage (RM) as two or more pregnancies loss.[1] Many women with a history of RM may go on to carry a pregnancy beyond 24 weeks, but it remains controversial whether these pregnancies are at higher risk in later stages of pregnancy. There is a need for evidence-based counselling for obstetric and perinatal outcomes in the subsequent pregnancy for Hong Kong women with a history of RM.

The Clinical Data Analysis and Reporting System (CDARS) in Hong Kong provides clinical information for management decision, clinical audit, research, and data analysis. This study aims to examine if any adverse obstetric and perinatal outcomes are associated with a history of RM among women in Hong Kong.

Methods

Medical records of all women with a history of RM and singleton pregnancy who were admitted between January 2000 and December 2019 at the Department of Obstetrics and Gynaecology, the Prince of Wales Hospital, The Chinese University of Hong Kong were retrieved from CDARS. All women underwent maternal and paternal karyotyping, basal hormone profiling, prothrombotic screening and antiphospholipid antibody test, thyroid function and thyroid antibodies tests, and ultrasonography. All other women without a history of RM during the same period were included for comparison. Women with multiple pregnancies were excluded.

Maternal characteristics extracted included age, marital status, type of pregnancy (natural or assisted conception), gestational age at booking. Gestational age was estimated based on the first day of the last menstrual period in the women with regular cycle, but ultrasound estimate was preferred if the date was uncertain or had a discrepancy of >7 days. Obstetric outcomes in the subsequent pregnancy included gestational hypertensive disorders, antepartum haemorrhage, gestational diabetes, preterm labour, and the mode of delivery. Perinatal outcomes included gestational age at delivery, small for gestational age, large for gestational age, infant sex, Apgar scores at 1 and 5 min, admission rate to the neonatal unit, perinatal death, and genital anomalies. Diseases were coded using the International Classification of Diseases, 9th Revision, Clinical Modification. Data validation by reviewing individual electronic medical records demonstrated high coding accuracy for diagnosis.

Analyses were performed using the SPSS (Windows version 25; IBM Corp, Armonk [NY], US). Comparisons between groups were made using the Student's *t* test, ANOVA, or non-parametric test for continuous variables and Chi-squared test or Fisher's exact test for categorical variables. Univariable logistic regression analyses and multivariable stepwise logistic regression analyses were performed, adjusting for baseline differences between groups. A P value of <0.05 was considered statistically significant.

Results

Of 111 124 women with singleton pregnancy included for analysis, 3112 (2.8%) had a history of two or more miscarriages and 108 012 (97.2%) did not (Table 1). Of the 3112 women with a history of

RM, 697 (22.4%) had primary RM and 2415 (77.6%) had secondary RM.

Women with a history RM had significantly increased odds of gestational hypertension (odds ratio [OR]=1.28) and Caesarean section (OR=1.47). After adjusting for maternal age, type of pregnancy, and gestational age at booking, only Caesarean section remained significant (adjusted OR=1.55, Table 2).

Women with a history of RM had higher rates of preterm delivery (OR=1.67), small for gestational age (OR=1.64), and perinatal death from all causes (OR=1.48), even after adjusting for confounders (adjusted OR=1.72, 1.70, and 1.52, respectively) [Table 3].

TABLE 1. Characteristics of participants

Characteristic	Recurrent miscarriage (n=3112)*	Control (n=108 012)*	P value
Maternal age, y			<0.001
<20	21 (0.7)	5562 (5.1)	-
20-29	691 (22.2)	37804 (35.0)	-
30-39	1979 (63.2)	57246 (53.0)	-
>40	421 (13.5)	7400 (6.9)	-
Body mass index, kg/m^2	22.3±3.8	22.9±4.2	0.058
Type of pregnancy			<0.001
Natural conception	2552 (82.0)	96932 (90.0)	-
Assisted conception	560 (18.0)	11080 (10.0)	-
Gestational age at booking, wk			<0.001
<12	1408 (45.2)	44284 (41.0)	-
12-20	1556 (50.0)	56166 (52.0)	-
>20	148 (4.8)	7562 (7.0)	-

* Data are presented as mean ± standard deviation or No. (%) of participants

Discussion

Women with a history of RM are at higher risk of several adverse obstetric and perinatal outcomes including preterm labour, Caesarean section, small

TABLE 2. Obstetric outcomes

Obstetric outcome	No. (%) of participants		Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	Recurrent miscarriage (n=3112)	Control (n=108 012)		
Gestational hypertension	154 (4.9)	4221 (3.9)	1.28 (1.09-1.51)*	1.14 (0.98-1.28)
Preeclampsia	24 (0.8)	688 (0.6)	1.21 (0.81-1.82)	1.17 (0.77-1.93)
Eclampsia	4 (0.1)	121 (0.1)	1.15 (0.42-3.1)	1.10 (0.35-3.77)
Antepartum haemorrhage	101 (3.2)	3212 (3.0)	1.09 (0.90-1.34)	1.04 (0.72-1.43)
Gestational diabetes	156 (5.0)	4921 (4.6)	1.12 (0.98-1.31)	1.08 (0.92-1.41)
Operative vaginal delivery	291 (9.4)	10092 (9.3)	1.00 (0.89-1.13)	1.00 (0.98-1.14)
Caesarean section	827 (26.6)	21312 (19.7)	1.47 (1.36-1.60)*	1.55 (1.32-1.77)*

* P<0.05

TABLE 3. Perinatal outcomes

Perinatal outcome	No. (%) of participants		Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	Recurrent miscarriage (n=3112)	Comparison group (n=108 012)		
Infant sex			1.11 (1.04-1.20)	-
Female	1608 (51.7)	52926 (49.0)	-	-
Male	1504 (48.3)	55086 (51.0)	-	-
Preterm birth	252 (8.1)	5400 (5.0)	1.67 (1.47-1.91)*	1.72 (1.50-1.99)*
Small for gestational age	150 (4.8)	3229 (3.0)	1.64 (1.39-1.94)*	1.70 (1.41-1.98)*
Large for gestational age	109 (3.5)	3886 (3.6)	0.97 (0.80-1.18)	1.01 (0.79-1.24)
Apgar score <7 at 1 min	89 (2.9)	3080 (2.9)	1.00 (0.81-1.24)	1.02 (0.80-1.25)
Apgar score <7 at 5 min	35 (1.1)	1100 (1.0)	1.11 (0.79-1.56)	1.01 (0.70-1.49)
Admission to neonatal unit	404 (13.0)	14022 (13.0)	1.00 (0.90-1.11)	1.01 (0.83-1.20)
Perinatal death	31 (1.0)	728 (0.7)	1.48 (1.03-2.12)*	1.52 (1.11-2.32)*
Congenital anomalies	28 (0.9)	746 (0.7)	1.30 (0.89-1.90)	1.21 (0.71-2.19)

* P<0.05

for gestational age, and perinatal death. More intensive antenatal monitoring is required for this group of women.

In a large epidemiological study of pregnancy outcomes between women with a previous miscarriage and women with a previous successful pregnancy, women with primary miscarriage were at significant higher risk of pre-eclampsia, antepartum haemorrhage, and low birth weight in the subsequent pregnancy.[2]

A history of RM has been reported to associate with preterm delivery, perinatal death, and delivery by Caesarean section, but the sample size of the study was small. However, in a study of 42 women, no significant difference in the risk of developing growth restriction, delivery by Caesarean section, or perinatal death was reported between women with unexplained RM and controls.[3] Another study of women with RM did not adjust for the effects of confounders.[4]

Although we demonstrated a significantly increased risk of several obstetric and perinatal adverse outcomes in women with a history of RM, RM can be caused by a heterogeneous group of conditions, some of which can be associated with an increased risk of pregnancy complications, and thus there is a potential bias owing to these confounders. Women with unexplained RM is most suitable for examining pregnancy outcomes, because the confounding effects of other pathologies is minimised.

There are several limitations to the present study. The Prince of Wales Hospital is a tertiary referral hospital, and the control group may be slightly skewed towards higher pregnancy risk. Study population was mainly Chinese and may not be compared with other ethnic populations. Owing to the retrospective nature of the study, some clinical parameters including detailed paternal information may be missing.

Conclusions

Chinese women with a history of two or more miscarriages have an increased risk of several obstetric and perinatal complications.

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