

PERINATAL EPIDEMIOLOGY

Induced abortion and risk of subsequent miscarriage

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Background To evaluate the impact of surgically induced first-trimester abortion on the risk of miscarriage in a subsequent pregnancy.

Methods The study is a pregnancy cohort study. It was conducted among 15 general hospitals or maternity and infant health institutes in Shanghai, China from November 1993 to March 1998. The abortion cohort consisted of pregnant women whose previous pregnancies were terminated by vacuum aspiration (98%). The reference cohort consisted of primigravidae. Subjects were recruited at 35–63 days of gestational age. A total of 2953 pregnant women were enrolled; 1502 in the abortion cohort, 1451 in the reference cohort.

Results There were only 62 women lost to follow-up. The remaining 2891 women had 2732 live births, and 137 miscarriages. About 5.5% of pregnancies in the abortion cohort were miscarried and 4.0% in the reference cohort. Once potential confounders were controlled for by logistic regression, odds ratio (OR) of miscarriage between the abortion cohort and the reference cohort was 1.55 (95% CI: 1.08–2.23). The adjusted OR were 2.44 (95% CI: 1.16–5.15) among women who were recruited within 49 days of gestational age, and 1.72 (95% CI: 1.09–2.72) for the first-trimester miscarriage.

Conclusions Induced abortion by vacuum aspiration is associated with an increased risk of first-trimester miscarriage in the subsequent pregnancy.

Keywords Pregnancy-based cohort study, induced abortion, vacuum aspiration, miscarriage, primigravidae

Induced abortion is used worldwide to terminate unwanted pregnancies. In China, vacuum aspiration is a major technique to end first-trimester pregnancies. This technique is believed to be relatively safe—little trauma is caused to the cervix and uterus. Such a conclusion is supported by a number of studies,^{1–3} but is surrounded by much controversy. For instance, a recent large-scale Danish study showed an increased risk of miscarriage following prior induced abortion among women who got pregnant within 3 months after the abortion.⁴ Since 50 million abortions may occur worldwide annually,⁵ even a small adverse effect may be of public health importance. In this paper, we used the

data from a cohort study to re-evaluate the relationship between miscarriage and prior induced abortion.

Methods

This is a pregnancy cohort study, which was conducted between November 1993 and March 1998. The study method was described elsewhere.⁶ Here is brief introduction of the research procedure.

Two study cohorts were recruited at 15 general hospitals or maternity and infant health institutes in Shanghai during the study period. One is an abortion cohort, consisting of pregnant women whose previous pregnancies were terminated by surgically induced abortion within 3 months of gestational age. The other is a reference cohort, consisting of primigravidae (to control for parity). Those who had any other pregnancy history (i.e. stillbirth, miscarriage, ectopic, molar pregnancy, and live birth) were excluded in this study. Pregnancy was detected by means of an assay for urinary chorionic gonadotropin (hCG). Women presenting for antenatal care at any of the participating health facilities were considered for inclusion in the study. Women were invited

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to participate in the study if no more than 63 days had elapsed since the first day of their last normal menses. Only currently married women were enrolled in order to get reliable information on abortion history. No eligible women refused to participate in this study. Participants gave their informed consent at the first interview, and were then questioned by trained interviewers. Information on demographic characteristics, contraceptive use, reproductive events (including induced abortion history), disease history, and exposure to toxic chemicals etc were collected. Some underreporting of previous abortions may have occurred, but this was expected to be minor because Chinese women would be motivated to accurately report their medical history in order to have a healthy child (the majority of couples in urban areas have only one child). Implication of such underreporting is further discussed in the Discussion.

However, since there were fewer eligible cases than controls, we modified the enrolment procedure from January 1997; recruiting a woman for the control group only after two cases had been recruited.

After the first interview, these participants were scheduled for follow-up at the 16th, 24th, 32nd week of pregnancy, and the 42nd day after delivery, respectively. Maternal weight gain, injury, blood pressure, pregnancy complications, and pregnancy outcomes were recorded at each interview.

A total of 2953 pregnant women were recruited in this study; 1502, or 50.9%, had prior history of induced abortion. Of these, 1235 (82.2%) experienced one abortion, and 267 (17.8%) had two or more. Nearly 98% of these pregnancies were terminated by vacuum aspiration. About 84% of induced abortions were due to unwanted pregnancies, and 16% due to diseases during the first trimester of pregnancy.

In China, the widely accepted definition of miscarriage is pregnancy spontaneously ended before 28 weeks of gestation,⁷ in contrast to 20 weeks more typically used elsewhere.⁸ The former definition is used in this paper. The first-trimester miscarriage is defined as pregnancy aborted within 14 gestational weeks from last menstrual period, and the late miscarriage refers to abortion between 14 and 28 gestational weeks.⁹

Life-table analyses were used to calculate rates of miscarriage in both abortion and reference cohorts. Logistic regression analyses were used to yield an adjusted risk of miscarriage by controlling for maternal age, education, occupation, family income, body mass index (BMI), diseases during pregnancy, smoking, alcohol and coffee consumption one month before recruitment, toxic exposure, conception season, and calendar year at recruitment. Data were also stratified by gestational age at recruitment (35–49 days, 50–56 days, 57–63 days). The risk of miscarriage was re-analysed at each level of gestational age by logistic regression. The first-trimester and second-trimester miscarriages were also of interest, and the risk of each type of miscarriage was estimated by logistic regression. Moreover, we used the Mantel-Haenszel method to re-analyse the risk of miscarriage stratifying the data by days of gestational age at recruitment. The first- and second-trimester miscarriages were also re-analysed by a similar method. Since women in the abortion cohort were recruited at somewhat greater gestational age than women in the control cohort, those recruited before 50 days of gestational age were also re-analysed using the Mantel-Haenszel method. SPSS 9.0 and SAS 6.12 software packages were used for these analyses.

Results

Among 2953 participants, 62 (2.1%) were lost to follow-up; 38 in the abortion cohort and 24 in the reference cohort. There was no difference in the loss of follow-up between the two cohorts ($P = 0.1$).

Table 1 shows percentage of participants by women's characteristics and by cohorts. The distribution of gestational age at recruitment, maternal occupation, family income, conception season, and calendar year at recruitment were significantly different between the two cohorts. For instance, there were more women in the reference cohort who were recruited before 57 days of pregnancy than in the exposed cohort. Nearly three in five women in the reference cohort were recruited before June 1995, which is more than that in the abortion cohort (43%) during the same period, due mainly to a change of enrolment procedure in 1997. For the same reason, more exposed women were recruited in winter and spring than non-exposed women. Non-exposed women were also more likely to have a white-collar job, with higher income, than exposed women.

Nearly 5.5% (80/1464) of pregnancies in the abortion cohort ended in miscarriage, compared with 4.0% (57/1427) in the reference cohort. This proportion declined with the increasing gestational age at recruitment—13.0% of those recruited before 50 days of gestation, 8.3% between 50 and 56 days, and 3.6% between 57 and 63 days in the abortion cohort; for the reference cohort these figures were 7.4%, 6.0%, and 2.7%, respectively.

Since miscarriage is a time-dependent event, life-table analysis was used to compare the probabilities of miscarriage between abortion and reference cohorts at different gestational ages. When including all participants, the probability of miscarriage started to be higher in the abortion cohort than in the reference cohort at 12 gestational weeks (Figure 1). However, the difference became apparent at 9 gestational weeks among women who were recruited before 50 days of gestational age (Figure 2).

Table 2 shows the adjusted odds ratio (OR) of miscarriage after controlling for some potential confounders: maternal age, education, occupation, family income, BMI, diseases during pregnancy, smoking, alcohol and coffee consumption one month before recruitment, toxic exposure, conception season, and calendar year at recruitment. Women with a history of abortion were at an increased risk of miscarriage. For those who had only one prior induced abortion, the adjusted OR was 1.60 (95% CI: 1.10–2.33). For women who had one or more abortions, the adjusted OR was 1.55 (95% CI: 1.08–2.23). Data were also stratified by gestational age at recruitment (middle of Table 2) and by type of miscarriage (right hand of Table 2), and the association was then re-analysed. The association no longer existed in subgroups recruited after 49 gestational days, but remained among women recruited before 50 gestational days. Moreover, prior induced abortion only increased the risk of first-trimester miscarriage, but not the risk of second-trimester miscarriage.

In agreement with the logistic regression results, Mantel-Haenszel analysis showed prior history of induced abortion was significantly associated with increased risk of miscarriage (<28 weeks of gestational age) and first-trimester miscarriage (<14 weeks of gestational age) (Table 3). Among women who were recruited before 50 days of gestational age, there is a borderline significant association between abortion history and

Table 1 Percentage of participants by maternal characteristics and study cohorts

Characteristics	Reference cohort (n = 1451)	Abortion cohort (n = 1502)	P-value
Maternal age at conception			
-25	45.4	43.1	P = 0.21
25-29	44.1	44.5	
30+	10.5	12.4	
Maternal education			
-Middle school	25.9	28.8	P = 0.21
High school	50.4	47.9	
College+	23.6	23.3	
Maternal occupation			
White collar	38.7	34.4	P = 0.01
Blue collar	61.3	65.6	
Family income (Yuan/month)			
-1500	40.6	49.9	P < 0.001
1500+	59.4	50.1	
Toxic chemical exposure 6 months before pregnancy			
No	95.3	96.5	P = 0.11
Yes	4.7	3.5	
Habit of smoking or alcohol/coffee consumption			
No	94.1	94.8	P = 0.38
Yes	5.9	5.2	
Body mass index (kg/m²)			
-19.8	40.5	41.2	P = 0.80
19.8-25.9	57.3	56.3	
26.0+	2.2	2.5	
Disease during the pregnancy			
No	94.1	95.0	P = 0.30
Yes	5.9	5.0	
Gestational age at recruitment			
-49 days	14.0	11.3	P < 0.001
50-56 days	18.4	14.4	
57-63 days	67.6	74.3	
Calendar year at recruitment			
Before 31 May 31 1995	61.1	42.9	P < 0.001
After 31 May 1995	38.9	57.1	
Conception season			
Spring	20.1	24.0	P = 0.04
Summer	28.7	18.4	
Autumn	31.2	26.1	
Winter	20.0	31.5	

miscarriage; the relative risks were 1.95 and 1.68 for the first- and second-trimester miscarriage, respectively, but they were not significant at 0.05 level, possibly due to small sample size.

Discussion and Conclusion

The study indicates that a higher risk of miscarriage, particularly those occurring within the first 3 months of gestation, is associated with prior first trimester induced abortion. Since the majority of the abortions were terminated by vacuum aspiration, the conclusion could, thus, largely be attributed to this technique.

However, results from previous studies are conflicting. Daling and Emanuel reported a null association between prior induced abortion and miscarriage, but all of the cases and controls came from a single hospital.¹⁰ Although some potential confounders were matched (maternal age, socioeconomic status, previous fetal death, and pregnancy order), selection bias may still be a

feature of this study because cases from only one hospital are unlikely to be representative of all cases in the defined population. On the other hand, the authors did not give information on gestational age when analysing miscarriage. We do not know whether the gestational age at recruitment is controlled. Bias may occur if there is a difference in gestational age between comparison groups.

Another hospital-based case-control study conducted by Levin and colleagues indicated that multiple induced abortions increased the risk of subsequent first- and second-trimester miscarriage.⁹ Unfortunately, the authors failed to provide information on the abortion technique. All cases and controls were also from a single hospital. Moreover, only 32% of the hospital-admitted cases were available to be interviewed. Selection bias may thus occur in this study. Wright and co-workers reported a tenfold increase in the incidence of second-trimester abortion following vaginal termination of pregnancy.¹¹ Since only

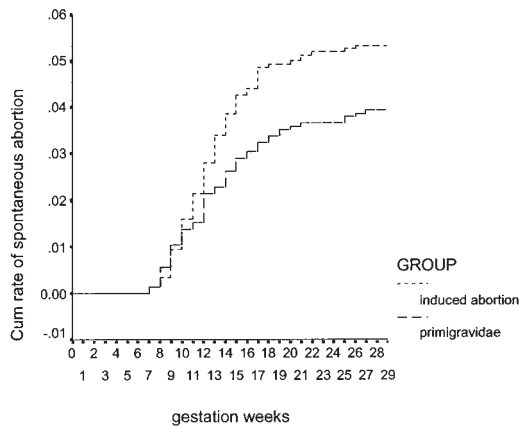


Figure 1 Cumulative abortion rates in the abortion cohort and the reference cohort recruited up to 63 days of gestation. Life-table analyses

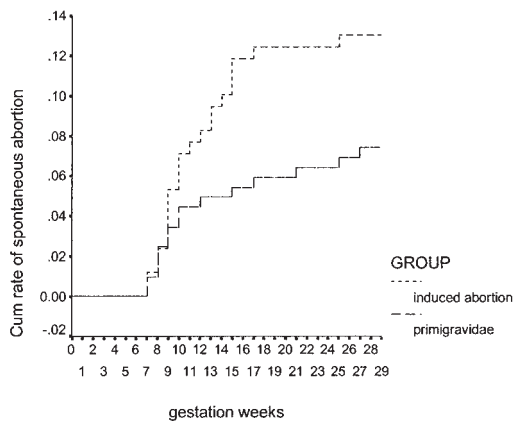


Figure 2 Cumulative abortion rates in the abortion cohort and the reference cohort recruited up to 49 days of gestation. Life-table analyses

maternal age was controlled in this study, other factors, such as pregnancy order and socioeconomic status, could confound the research result. The abortion technique was not reported. The authors indicated that all cases had had forcible dilatation of the cervix. Therefore, the association should not be attributed to the vacuum aspiration method.

A null association between abortion terminated by vacuum aspiration and midtrimester miscarriage was reported by a World Health Organization multicentre study.¹² However, this conclusion is questionable because of the small sample size. In a recent large study based on Danish national registries, an increased risk of miscarriage following an induced abortion (the majority were terminated by vacuum aspiration) was found among women who became pregnant within 3 months of the induced abortion.⁴ This association was not seen for those whose abortion was more than 3 months before their next pregnancy.

In our study, we recruited nearly 3000 participants from 15 hospitals. The sample size and number of hospitals involved

exceed those of most prior studies. This enables us to better establish the relationship between induced abortion and miscarriage, and reduce hospital selection bias. All participants were enrolled between 5 and 9 weeks of gestation, which enabled us to find early loss of pregnancy that other studies could not trace.^{10,12}

The way in which this study was conducted, however, gives rise to other concerns. First, Wilcox and co-workers reported that 22% of pregnancies were clinically unrecognized early loss, as compared with 9% which were clinically recognized.¹³ In our study, pregnancy was detected by means of enzyme immunoassay (EIA) for human chorionic gonadotropin (hCG), which was widely used in China during the study period. Subject enrolment depended on a woman going to see a hospital doctor after recognizing the pregnancy herself. Therefore, all miscarriages in our study were clinically recognized as a loss of pregnancy. We do not know if there is any difference in spontaneous abortion rate between women involved in the study and those not involved. Secondly, cases were recruited at later gestational age than controls. Since miscarriage is more likely to occur at an earlier gestational age,¹³ respondents in the exposed group were less likely to report a loss of pregnancy than unexposed women. Thirdly, abortion history might be underreported by respondents, although we employed some techniques to avoid recall bias, such as training interviewers, enrolling married women, and interviewing in a private environment. As a consequence, the research result would bias towards the null. Finally, 90% of study subjects were under 30 years old. Women with previous adverse pregnancy outcomes were excluded from this study. In some ways, the participants of our study were relatively younger and healthier than the general population. This may partly explain the low overall miscarriage rate in this study.

Some mechanisms may link induced abortion terminated by vacuum aspiration to first-trimester miscarriage. Reproductive tract infections (RTI) may be one of the mechanisms. To some degree, induced abortion increases the risk of RTI.¹⁴ Some of these infections, such as herpes simplex and syphilis, have been associated with an increased incidence of spontaneous abortion in the first half of pregnancy.⁸ Implantation delay might be another mechanism. The mean time of implantation among conceptions which ended in live birth was reported to be 9.1 days after ovulation.¹⁵ In contrast, the time was 10.5 days for pregnancies that ended within 6 weeks after the last menstrual period. A strong increase in the risk of early pregnancy loss was related to late implantation. We suspect that the minor trauma caused to the uterus by induced abortion, as well as uterine infection, might delay the implantation of the embryo, and then result in miscarriage. This hypothesis is supported by the Danish study: the uterus is not completely recovered from the last induced abortion after a short interpregnancy interval, thus this abortion is associated with an increased risk of subsequent miscarriage.⁴ After a longer interpregnancy interval, the uterus is more likely to have recovered. As a result, the association no longer exists. Many gynaecologists argue that cervical incompetence leads to midtrimester miscarriage. Cervical incompetence is usually characterized by cervical dilatation in the second trimester or perhaps early in the third trimester. This effect is less apparent with vacuum aspiration.

Induced abortion has been legal in China since the 1960s. Wu and co-workers reported that about one-quarter of unmarried women in Shanghai had at least one prior induced

Table 2 Adjusted odds ratios (OR) of miscarriage following first-trimester surgically induced abortion (logistic regression)

History of induced abortion	All recruiters ^a		Gestational age at recruitment ^b			Type of miscarriage ^a	
	35–63 days OR (95% CI)	35–49 days OR (95% CI)	50–56 days OR (95% CI)	57–63 days OR (95% CI)	First trimester OR (95% CI)	Second trimester OR (95% CI)	
No (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00	
Once ^c	1.60 (1.10–2.33)	2.52 (1.15–5.51)	1.28 (0.58–2.82)	1.58 (0.93–2.69)	1.76 (1.10–2.82)	1.31 (0.72–2.39) ^d	
All (≥1) ^e	1.55 (1.08–2.23)	2.44 (1.16–5.15)	1.43 (0.68–2.98)	1.42 (0.84–2.38)	1.72 (1.09–2.72)	1.24 (0.70–2.22) ^f	

^a Covariates = maternal age (categories, three levels), maternal education (categories, three levels), maternal occupation (dichotomy), body mass index (categories, three levels), disease during pregnancy (dichotomy), habit of smoking or alcohol/coffee consumption one month before recruitment (dichotomy), exposure to toxic chemicals (dichotomy), family income/month (dichotomy), gestational age at recruitment (continuous variable), calendar year at recruitment (dichotomy), conception season (categories, four levels).

^b Covariates = maternal age (categories, three levels), maternal education (categories, three levels), maternal occupation (dichotomy), body mass index (categories, three levels), disease during pregnancy (dichotomy), habit of smoking or alcohol/coffee consumption one month before recruitment (dichotomy), exposure to toxic chemicals (dichotomy), family income/month (dichotomy).

^c In all, 267 women who had ≥2 induced abortions and 50 women who lost to follow-up were excluded.

^d Eighty first-trimester miscarriages were excluded.

^e Sixty-two women were excluded due to loss to follow-up.

^f Eighty-seven first-trimester miscarriages were excluded.

Table 3 Summary results of Mantel-Haenszel analyses stratified by gestational days

Response variables	Cohort	No.	% miscarriage	Adjusted RR ^a	95% CI
Gestational age at recruitment was up to 63 days					
First-trimester miscarriage	Exp. ^b	1464	3.62	1.72	1.14–2.61
	Non-exp. ^c	1427	2.38	1.00	–
Second-trimester miscarriage ^d	Exp.	1411	1.91	1.28	0.75–2.19
	Non-exp.	1393	1.65	1.00	–
Total	Exp.	1464	5.46	1.52	1.10–2.10
	Non-exp.	1427	3.99	1.00	–
Gestational age at recruitment was up to 49 days					
First-trimester miscarriage	Exp.	159	10.06	1.95	0.93–4.10
	Non-exp.	200	5.00	1.00	–
Second-trimester miscarriage ^e	Exp.	143	4.20	1.68	0.56–5.03
	Non-exp.	190	2.63	1.00	–
Total	Exp.	159	13.84	1.82	1.00–3.31
	Non-exp.	200	7.50	1.00	–

^a Relative risk.

^b Exp: induced abortion cohort.

^c Non-exp: primigravidae.

^d Eighty-seven first-trimester miscarriages were excluded.

^e Twenty-six first-trimester miscarriages were excluded.

abortion (premarital live birth is rare in China).¹⁶ From this, we estimate that about 15% of first-trimester miscarriages in Shanghai can be attributed to prior history of induced abortion. However, since the very early pregnancy losses were excluded from this research, further studies are needed, using very sensitive and specific assay to detect conception. Our study showed induced abortion by vacuum aspiration is associated with an increased risk of first-trimester miscarriage in the subsequent pregnancy.

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