

ORIGINAL ARTICLE

Medical Abortion and the Risk of Subsequent Adverse Pregnancy Outcomes

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ABSTRACT

BACKGROUND

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The long-term safety of surgical abortion in the first trimester is well established. Despite the increasing use of medical abortion (abortion by means of medication), limited information is available regarding the effects of this procedure on subsequent pregnancies.

METHODS

We identified all women living in Denmark who had undergone an abortion for non-medical reasons between 1999 and 2004 and obtained information regarding subsequent pregnancies from national registries. Risks of ectopic pregnancy, spontaneous abortion, preterm birth (at <37 weeks of gestation), and low birth weight (<2500 g) in the first subsequent pregnancy in women who had had a first-trimester medical abortion were compared with risks in women who had had a first-trimester surgical abortion.

RESULTS

Among 11,814 pregnancies in women who had had a previous first-trimester medical abortion (2710 women) or surgical abortion (9104 women), there were 274 ectopic pregnancies (respective incidence rates, 2.4% and 2.3%), 1426 spontaneous abortions (12.2% and 12.7%), 552 preterm births (5.4% and 6.7%), and 478 births with low birth weight (4.0% and 5.1%). After adjustment for maternal age, interval between pregnancies, gestational age at abortion, parity, cohabitation status, and urban or non-urban residence, medical abortion was not associated with a significantly increased risk of ectopic pregnancy (relative risk, 1.04; 95% confidence interval [CI], 0.76 to 1.41), spontaneous abortion (relative risk, 0.87; 95% CI, 0.72 to 1.05), preterm birth (relative risk, 0.88; 95% CI, 0.66 to 1.18), or low birth weight (relative risk, 0.82; 95% CI, 0.61 to 1.11). Gestational age at medical abortion was not significantly associated with any of these adverse outcomes.

CONCLUSIONS

We found no evidence that a previous medical abortion, as compared with a previous surgical abortion, increases the risk of spontaneous abortion, ectopic pregnancy, preterm birth, or low birth weight.

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THE TERMINATION OF EARLY PREGNANCY with medication (i.e., medical abortion) can be traced back to 1950,¹ but effective drug regimens with limited known side effects were developed fairly recently, providing an alternative to surgical abortion. Currently, there are three available regimens for medical abortion: misoprostol alone, methotrexate followed by misoprostol, and, by far the most commonly used method, mifepristone followed by misoprostol. By 2000, more than 3 million women worldwide had used mifepristone in combination with misoprostol,¹ and in certain areas of the world, such as France, Scotland, and Sweden, more than half of early first-trimester abortions were performed with this method.² The Food and Drug Administration gave full approval for the marketing of mifepristone for medical abortion in 2000. By 2004, approximately 360,000 women in the United States had had an abortion with this method,³ and its use is increasing.

Many studies have concluded that surgical abortion in the first trimester does not increase the risk of ectopic pregnancy, spontaneous abortion, preterm birth, or low birth weight in subsequent pregnancies.^{4,5} Medical abortion has generally minor short-term side effects, most often related to misoprostol (gastrointestinal side effects, feelings of warmth, or chills). Severe complications, which are rare, include hemorrhage and endometritis, each with an incidence of less than 1%.⁶ However, data on the effects of medical abortion on subsequent pregnancies are scarce.

Ectopic pregnancy is the leading cause of pregnancy-related death in the first trimester and accounts for about 9% of all pregnancy-related deaths in the United States.⁷ One population-based case-control study on risk factors for ectopic pregnancy⁸ found a significantly increased risk for ectopic pregnancy associated with medical abortion, but not surgical abortion, as compared with women with no history of abortion. However, the study included only a small number of women who had history of medical abortion (13 case patients and 11 controls).

Given that the medical abortion procedure is increasingly used worldwide, we used Danish nationwide cohort data to determine whether there is a higher risk of ectopic pregnancy, spontaneous abortion, low birth weight, or preterm birth in the first pregnancy after a medical abortion as compared with a surgical abortion.

METHODS

DATA SOURCES

Medical abortion with mifepristone and misoprostol became available in Denmark in December 1997,⁹ and it has been commonly used since 1998. The Danish National Induced Abortion Registry has kept computerized records of all induced abortions performed in the country since 1973. We identified all women living in Denmark who had had an abortion for nonmedical reasons between 1999 and 2004. Surgical and medical procedures were coded separately, and the type of drugs used (mifepristone, misoprostol, and other prostaglandin analogues) and their dosages were also recorded. Information was obtained from this registry on the date of abortion and the gestational age and maternal age at the time of the abortion. To obtain information regarding subsequent pregnancies, data for each woman were linked through her personal civil registration number to the Danish National Birth Registry and the Danish National Patient Registry up to 2005. The Danish National Birth Registry has collected data since 1968 for the primary purpose of monitoring the health of newborns and the quality of antenatal care, although the data are increasingly being used for research.¹⁰ The data are provided by the midwife or physician responsible for the delivery. Information regarding the outcome of the subsequent pregnancy, including gestational age at birth, birth weight, parity, and maternal age, as well as whether the birth was a live birth or stillbirth, was also obtained from the birth registry. Low birth weight was defined as a weight below 2500 g at birth, and preterm birth as birth before 37 completed weeks of gestation.

Information regarding ectopic pregnancy and spontaneous abortion was obtained from the Danish National Patient Registry, which contains data on all hospital stays and outpatient visits for the entire study period. For each admission or visit, the patient registry collects information on the primary diagnosis (the diagnosis that best describes the condition leading to the admission or outpatient visit and that is the primary reason for the prescribed and completed course of tests and treatments) and up to 20 subsidiary diagnoses. The patient registry also contains information on dates of outpatient visits and admission and discharge dates. Data were extracted with the use of *Inter-*

national Classification of Diseases, 10th Revision, codes¹¹ and were linked by the Danish Medical Council according to our study protocol; the data were stripped of personal identifiers before being released for analysis.

To validate the quality of our data, we compared information from the Danish National Birth Cohort with the data from the birth registry. The Danish National Birth Cohort is a prospective study of approximately 100,000 women recruited during early pregnancy.¹² Women were interviewed at enrollment and followed throughout their pregnancies. Information from both data sources was available for a total of 96,415 women. There was a high level of agreement between the two sources of birth data. For example, the recorded first day of the last menstrual period varied by no more than 1 week for 94% of the women; the gestational age at delivery varied by no more than 1 week for 90% of the women and by no more than 2 weeks for 95%. There was also a high level of agreement with respect to parity and maternal residence (kappa value, 0.96 for both).

ELIGIBILITY AND GROUP ASSIGNMENTS

Women who had undergone an induced abortion for nonmedical reasons and had subsequently become pregnant were eligible for the study. We excluded women who had had an abortion within 30 days after the diagnosis of an ectopic pregnancy (on the assumption that the abortion was performed to treat the ectopic pregnancy) and women for whom the interval between the abortion and the subsequent pregnancy was less than 30 days. If a woman had had more than one abortion before the subsequent pregnancy, the abortion that was closest in time to the subsequent pregnancy was used for classifying the type of abortion (medical or surgical) and determining the interpregnancy interval. Women could enter the cohort more than once during the study period if they had more than one abortion followed by a pregnancy; this situation accounted for only 1.1% of eligible women.

Women were assigned to the medical-abortion group if the abortion was performed with the use of mifepristone followed by misoprostol or with misoprostol alone and were assigned to the surgical-abortion group if the abortion was conducted by means of surgery alone. Abortions that required

both medical and surgical intervention were defined as medically induced, on the assumption that the intent was to induce an abortion by medical means. Mifepristone is used for up to 63 days after the last menstrual period¹³; therefore, women who underwent surgical abortion after 9 weeks of gestation were excluded from the analysis.

The study was approved by the Danish National Board of Health, the Danish Data Protection Agency, and the institutional review boards of the University of California at Los Angeles and the National Institutes of Health. Informed consent was not required.

STATISTICAL ANALYSIS

Logistic regression, performed with PROC GENMOD (SAS, version 9.1) for dichotomous outcomes, was used to determine relative risks and 95% confidence intervals for ectopic pregnancy, spontaneous abortion, preterm birth, and low birth weight among women who had had a medical abortion as compared with those who had had a surgical abortion. A multiple linear regression model was used for continuous outcomes (gestational age at birth and birth weight). Both models were adjusted for gestational age at the time of the abortion and the interval between the abortion and the subsequent pregnancy, as well as for maternal age and parity, maternal residence (classified as urban for women who lived in Copenhagen, Aarhus, Aalborg, or Odense and as nonurban otherwise), and partner-cohabitation status — all at the time of the subsequent pregnancy.

RESULTS

The abortion registry listed 30,349 women who had had an abortion for nonmedical reasons between 1999 and 2004. Of these women, 16,883 had one or more pregnancies after the abortion. In total, these women had 17,170 subsequent pregnancies, of which 5170 were excluded from the analysis because the previous abortion had been induced after 9 weeks of gestation, 70 because data were missing on gestational age at the time of the abortion, and 116 because the interpregnancy interval was 30 days or less. The remaining 11,814 pregnancies in 11,682 women formed the basis for our analysis. Among these pregnancies, there were 10,018 (84.8%) live births, 1486 (12.6%) spontane-

ous abortions, 36 (0.3%) stillbirths, and 274 (2.3%) ectopic pregnancies.

Table 1 shows the demographic and clinical characteristics of the women. The 189 women who underwent surgical abortion after medical abortion failed (6.9% of the study populations) were included in the medical-abortion group. We found significant differences between the medical-abortion and surgical-abortion groups with respect to maternal age, interpregnancy interval, residence, and gestational age at the time of abortion but not with respect to partner cohabitation status or parity.

The incidence of a subsequent ectopic pregnancy in the medical-abortion and surgical-abortion groups was 2.4% and 2.3%, respectively. After adjustment for maternal age, parity, interpregnancy interval, maternal residence, cohabitation status, and gestational age at the time of the abortion, the risks of an ectopic pregnancy, spontaneous abortion, preterm birth, or low birth weight after a medical abortion did not differ significantly from the risks after a surgical abortion (Table 2). There were no significant differences between the two groups in the mean gestational age at birth or the mean birth weight. The gestational age at the time of the abortion was not significantly associated with any of the adverse outcomes (data not shown). The limited number of stillbirths did not permit meaningful analysis.

DISCUSSION

Our study shows that medical abortion, as compared with surgical abortion, is not associated with an increased risk of ectopic pregnancy, spontaneous abortion, low birth weight, or preterm birth in the first pregnancy after the abortion. It differs in several respects from a prior study by Bouyer and colleagues, which showed a significant association between medical abortion and ectopic pregnancy.⁸ We used a population-based cohort, whereas the previous findings reported were from population-based case patients and controls. In our study, the abortion information was obtained from a clinical registry, whereas abortion information was self-reported in the previous study. Our study included a large number of women who had had a medical abortion, providing 90% power to detect a minimal relative risk of 1.5 and almost

Table 1. Characteristics of Women Who Had an Induced Abortion for Nonmedical Reasons between 1999 and 2004 and a Subsequent Pregnancy between 1999 and 2005.*

Characteristic	Medical Abortion (N=2710)	Surgical Abortion (N=9104)	P Value
	<i>number of women (percent)</i>		
Maternal age			<0.001
≤19 yr	56 (2.1)	333 (3.7)	
20–24 yr	467 (17.2)	1890 (20.8)	
25–29 yr	817 (30.1)	2794 (30.7)	
30–34 yr	828 (30.6)	2609 (28.7)	
35–39 yr	447 (16.5)	1248 (13.7)	
≥40 yr	95 (3.5)	230 (2.5)	
Parity†			0.22
0	966 (43.1)	3422 (45.3)	
1	694 (31.0)	2310 (30.6)	
2	408 (18.2)	1293 (17.1)	
≥3	174 (7.8)	532 (7.0)	
Interpregnancy interval			<0.001
<1 yr	249 (9.2)	827 (9.1)	
1–2 yr	1130 (41.7)	3282 (36.1)	
3–4 yr	1130 (41.7)	3776 (41.5)	
>4 yr	201 (7.4)	1219 (13.4)	
Residence			<0.001
Urban	716 (26.4)	2911 (32.0)	
Nonurban	1994 (73.6)	6193 (68.0)	
Living with partner‡			0.10
Yes	1840 (79.7)	6019 (78.1)	
No	469 (20.3)	1690 (21.9)	
Gestational age of fetus at abortion			<0.001
≤5 wk	211 (7.8)	215 (2.4)	
6 wk	986 (36.4)	925 (10.2)	
7 wk	943 (34.8)	2098 (23.0)	
8 wk	475 (17.5)	3154 (34.6)	
9 wk	95 (3.5)	2712 (29.8)	

* With the exception of gestational age at the time of the abortion, all data refer to the time of the first pregnancy after the abortion. P values were calculated with the chi-square test.

† Data on parity refer to women with live birth or stillbirth; values were missing for 72 women in the medical-abortion group and 183 in the surgical-abortion group.

‡ Data on partner cohabitation status refer to women with live birth or stillbirth; values were missing for 5 women in the medical-abortion group and 31 in the surgical-abortion group.

Table 2. Pregnancy Outcomes.*

Outcome	Medical Abortion	Surgical Abortion	Relative Risk or Difference (95% CI)†	
			Unadjusted	Adjusted‡
Live birth — no./total no. (%)	2309/2710 (85.2)	7709/9104 (84.7)	—	—
Ectopic pregnancy — no./total no. (%)	65/2710 (2.4)	209/9104 (2.3)	1.04 (0.79 to 1.40)	1.07 (0.78 to 1.48)
Spontaneous abortion — no./total no. (%)	331/2710 (12.2)	1155/9104 (12.7)	0.96 (0.86 to 1.08)	0.87 (0.72 to 1.05)
Mean gestational age at birth — wk	39.4±2.0	39.3±2.1	0.10 (−0.02 to 0.23)	0.33 (−0.10 to 0.76)
Preterm birth — no./total no. (%)	101/1873 (5.4)	451/6704 (6.7)	0.80 (0.65 to 0.99)	0.88 (0.66 to 1.18)
Mean birth weight — g	3476±584	3454±603	22 (−12 to 55)	11 (−15 to 37)
Low birth weight — no./total no. (%)	92/2273 (4.0)	386/7628 (5.1)	0.80 (0.64 to 1.00)	0.82 (0.61 to 1.11)
Stillbirth — no./total no. (%)	5/2710 (0.2)	31/9104 (0.3)	—	—

* Plus–minus values are means ±SD. Spontaneous abortions were defined as pregnancies miscarried before 24 weeks of gestation. Data on mean gestational age and preterm birth are for live births only; data were missing for 436 women in the medical-abortion group and 1005 in the surgical-abortion group. Preterm birth was defined as birth at less than 37 weeks of gestation. Data on mean birth weight and low birth weight are for live births only; data were missing for 36 women in the medical-abortion group and 81 in the surgical-abortion group. Low birth weight was defined as a weight of less than 2500 g. Stillbirths were defined as pregnancies that resulted in stillbirths at 24 or more weeks of gestation.

† The surgical-abortion group was the reference group.

‡ Analyses were adjusted for maternal age, interpregnancy interval, gestational age at abortion, parity, cohabitation status, and maternal residence. Analysis of birth weight was also adjusted for gestational age at birth.

100% power to detect the relative risk of 2.8 that was reported in the previous study for ectopic pregnancy. However, the previous study included data from in-depth personal interviews that were unavailable in our registries; it also included a larger number of ectopic pregnancies.

Our findings on low birth weight and preterm birth are consistent with the results of a multicenter cohort study from China,¹⁴ which evaluated pregnancy outcomes in nulliparous women with no history of induced abortion (4925 women), those with one previous mifepristone-induced abortion (4931 women), and those with one previous surgical abortion (4800 women). The type of previous abortion was assigned on the basis of self-reported data. The authors found that a previous medical abortion did not increase the risk of low birth weight or preterm birth, as compared with no previous abortion or a previous surgical abortion.

Although we adjusted our estimates for several variables, we did not adjust them for maternal smoking, history of sexually transmitted diseases, or history of ectopic pregnancy, since information

on these variables was not available in our databases. Whereas each of these factors has been associated with an increased risk of ectopic pregnancy,^{7,15} we are unaware of any data suggesting that these variables are associated with the choice (or physician's recommendation) of the abortion method, and women in Denmark have equal access to health care services, with no out-of-pocket cost. We consider these variables unlikely to be confounders in our analysis.¹⁶

We chose not to compare women who had medical abortions directly with women who had no prior abortions, since these groups differ with respect to factors that affect pregnancy outcomes, such as socioeconomic status, smoking status, and other health-related conditions and behaviors.¹⁷ The implications of our data for the long-term safety of medical abortion therefore rely on the premise that surgical abortion in the first trimester is safe, which is supported by the majority of studies in the literature. A review of available data published in 1990 concluded that early surgical abortion by vacuum aspiration, currently the most commonly used method, was not associated with

ectopic pregnancy, spontaneous abortion, low birth weight, or preterm birth in a subsequent pregnancy.⁴ Most studies published since then have supported this conclusion.^{5,8,14,17-25} Among studies reporting increased risks of adverse outcomes in subsequent pregnancies,²⁶⁻³⁰ the findings have been inconsistent; this inconsistency may reflect the performance of multiple comparisons or recall bias in case-control studies of induced abortion and ectopic pregnancies and the use of older methods for abortion in some cases.

Because our study drew from the entire population of Denmark during the study period and because follow-up was almost complete, the study was not susceptible to selection bias. The large sample also provided sufficient power to detect a small effect, if one truly existed. The incidences of spontaneous abortion (12.6%), ectopic pregnancy

(2.3%), and stillbirth (0.3%) in our study population were within the ranges reported in the literature.³¹ The rate of failed medical abortion, defined as medical abortion followed by a surgical procedure (6.9% in our Danish study population), is also consistent with the rates in previous clinical trials³² and in a hospital-based study in Denmark.⁹ These observations support the validity of our data.

Our nationwide cohort study provides evidence that medical abortion is at least as safe as surgical abortion with respect to the risks of ectopic pregnancy, spontaneous abortion, low birth weight, and preterm birth in the first subsequent pregnancy.

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