Risk of surgical evacuation and risk of major surgery following second-trimester medical abortion in Denmark: A nationwide cohort study ☆

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1. Introduction

Medical termination of second-trimester pregnancies with mifepristone and misoprostol is an effective and acknowledged abortion procedure [1]. However, subsequent surgical evacuation is sometimes required for complete expulsion. Reported frequency

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of surgical evacuation following medical termination of second-trimester pregnancies varies between 3% and 55% in studies using the same medical induction regime [2–5]. Limited research exists on risk factors for surgical evacuation following second-trimester medical abortion [3,4]. Increasing maternal age, history of curettage, and fetal indication for termination have been suggested to increase the risk of surgical evacuation [3,4]. However, it remains unknown if different distributions of these and other potential risk factors bear the main responsibility for the variation in frequency of surgical evacuation reported in the literature.

In Denmark, where medical induction with mifepristone and misoprostol is the standard termination procedure of second-trimester pregnancies, annual quality assessment reports have also shown a significant variation in the risk of subsequent surgical evacuation among hospitals and a decline in risk throughout time, despite no difference in medical induction regimen and general handling of the procedure among the hospitals and no change in such throughout time [6,7].

Studies on the effectiveness of mifepristone/misoprostol in terminating second-trimester pregnancies have often been too small to study the safety of the procedure [8]. Thus, little is known about the risk of subsequent complications demanding major surgery.

Aiming primarily to recognize potential reasons for the major variation in risk of surgical evacuation following second-trimester medical abortions reported in the literature and observed in Denmark, we followed a Danish nationwide cohort of medical abortions induced in the second trimester with the objectives of (1) identifying risk factors for surgical evacuation, and (2) assessing the ability of these risk factors to explain the a priori observed variation in risk of surgical evacuation among Danish hospitals and the a priori observed decline throughout time.

Aiming secondarily to assess the safety of medical termination of second-trimester pregnancies, the third study objective was to assess the risk of major surgery in the study cohort.

2. Materials and methods

2.1. Study design

We conducted a register-based, historical cohort study, including all medical abortions induced in the second trimester during the period 2006–2017 among Danish women aged 15–49 years. All included abortions were followed for eight weeks from mifepristone administration.

2.2. Data sources

Using the specific diagnostic and treatment codes by which second-trimester medical abortions are registered in The Danish National Patient Register at induction, we were able to identify the cohort (Supplementary Table S1) [9]. Information on outcomes and explanatory variables of interest was extracted from The Danish National Patient Register, The Register of Legally Induced Abortions, and The Danish Medical Birth Register (Supplementary Table S1) [9–11].

A personal identification number given to all Danish citizens at birth or at immigration allowed reliable linkage of data between the different registers.

2.3. Medical abortion regimen

Throughout the study period, second-trimester medical abortion was provided according to a single national clinical guideline by 21 Danish gynecological hospital departments only [7]. The guideline makes evidence-based recommendations on all aspects of the procedure of second-trimester medically induced abortion, including medical regimen used for induction and indications for subsequent surgical evacuation. The guideline was developed by the Danish Society of Obstetrics and Gynecology in 2005 and revised in 2011 but did not change in its recommendation throughout the study period. The guideline is based on a review and grading of published evidence on medically induced second-trimester abortion [12].

Since 2006, medical induction has been the standard termination procedure of second-trimester pregnancies in Denmark. The recommended induction regimen has been 200 mg mifepristone followed 24–48 h later by 0.4 mg vaginally administrated misoprostol repeated every three hours to a maximum of 2 mg per day until expulsion. Due to lack of published evidence on when surgical evacuation is necessary for complete expulsion, the Danish guideline states that the decision to surgically intervene following medical induction is a clinical estimate that should be made by the gynecologist on duty and be based on observations of the post-abortion contraction state of the uterus, the amount of bleeding, and signs of retained placenta [7].

2.4. Outcomes of interest

Risk of surgical evacuation and risk of major surgery following medical induction were the two outcomes of interest. Both outcomes were assessed within the eight weeks of follow-up.

If a woman received either a uterine vacuum aspiration or a hysteroscopic excision of anticipated retained tissue following medical induction, she was considered to have experienced a surgical evacuation (Supplementary Table 1). The length of follow-up allowed assessment of both surgical evacuations done directly following the medical induction as well as those done secondarily. The timing of surgical evacuation was also assessed.

Major surgery was defined as surgery demanding the penetration of peritoneum. Information on all major surgeries was extracted, with no pre-defined restrictions.

2.5. Explanatory variables

Risk of surgical evacuation was assessed according to (a) year and (b) hospital of induction.

Furthermore, information on potential risk factors for surgical evacuation was extracted, including (a) gestational age, (b) maternal age, (c) history of induced abortion, (d) previous deliveries, and e) indication for termination.

2.6. Statistical analysis

In order to assess (1) whether or not gestational age, maternal age, previous deliveries, history of induced abortion, and indication for termination were risk factors for surgical evacuation following medical termination of second-trimester pregnancies and (2) if these potential risk factors were able to explain the a priori observed variation in risk of surgical evacuation among Danish hospitals and the a priori observed decline in risk throughout the study period, we fitted a multiple logistic regression model on the entire cohort, surgical evacuation (yes/no) being the outcome variable and the explanatory variables including: gestational age (categories: week 13/14/15/16/17/18/19/20/21/22/23), maternal age (years 15–19/20–24/25–29/30–34/35–39/40–44/45–49), previous medically induced abortions (yes/no), previous surgically induced abortions (yes/no), previous deliveries (only vaginal deliveries with spontaneous delivery of the placenta/at least one cesarean section/at least one manual removal of placenta), indication for termination (maternal health/fetal disease/social/unknown), year of induction (continuous variable), and hospital of induction

(Hosp1/. . ./Hosp21). For all variables, except the hospital variable, the category with the largest number of observations was chosen as the reference group. For the hospital variable, Copenhagen University Hospital (Hosp14) was chosen as the reference.

Reported were adjusted odds ratios (ORs) of surgical evacuation with 95% confidence intervals (CI). Linear trends were tested by entering the respective variables as numeric (one degree of freedom) in the multiple logistic regression model.

We did a quantitative bias analysis for the adjusted association between risk of surgical evacuation and year of induction as well as for the adjusted association between risk of surgical evacuation and hospital of induction. The purpose of the quantitative bias analysis was to estimate the size of a potential unmeasured risk factor, if this risk factor had to explain away the adjusted associations between risk of surgical evacuation and time/hospital of induction, respectively. Reported were the *E*-values for the OR of surgical evacuation of (1) the comparison of the first (2006) and last year (2017) of the study period and (2) the comparison of the hospital with the largest adjusted odds of surgical evacuation (not pre-defined) and Copenhagen University Hospital (Hosp14). According to the acknowledged definition, the *E*-value was defined as the minimum strength of association, on the OR scale, that an unmeasured risk factor would need to have with both surgical evacuation and year/hospital of induction, respectively, to fully explain away the association between these factors, conditional on gestational age, maternal age, previous medically induced abortions, previous surgically induced abortions, previous deliveries, and indication for termination [13].

Data on the occurrence of major surgery was reported descriptively.

Statistics were performed in SAS software, version 9.4 (SAS Institute).

3. Results

We identified 5702 medical abortions induced in the second trimester during the 12-year-long study period among women aged 15–49 years. Of these, 2934 (52%) underwent surgical evacuation within eight weeks from mifepristone administration.

The abortions peaked in nulliparas aged 25–34 years with no prior history of induced abortions (Table 1). The frequency of medical terminations was highest in the 15th gestational week and increased again in the 21st week after a decline (Table 1). Over half of the pregnancies were terminated based on fetal indication (Table 1).

Table 2 shows the adjusted OR of surgical evacuation according to gestational age, maternal age, history of reproductive events, indication for termination, year of induction, and hospital of induction. The risk of surgical evacuation declined almost linearly with increasing gestational age ($p < 0.001$, Table 2). Women aged 15–19 years had a reduced risk of surgical evacuation compared to older women (Table 2). Women with a history of only vaginal deliveries with spontaneous delivery of the placenta had a reduced risk of surgical evacuation compared to nulliparas (Table 2). The associations between surgical evacuation and history of other reproductive events were insignificant (Table 2). The indication for termination was also not associated to the risk of surgical evacuation (Table 2).

The proportion of surgical evacuations declined during the study period, from 64% in 2006 to 26% in 2017 (Fig. 1), while varying between 16% and 74% among the 21 hospitals (Table 1). The significant decline throughout time and the variation among hospitals persisted after adjusting for the identified risk factors (Table 2).

The minimum strength of association, on the OR scale, that an unmeasured risk factor would need to have with both surgical evacuation and hospital of induction to fully explain away the 2.38-fold increased odds of surgical evacuation at Hosp9 compared to the Copenhagen University Hospital (Hosp14, Table 2) was

Table 1
Number of abortions and subsequent surgical evacuations in Denmark from 2006-2017 according to the explanatory variables of interest.

	Abortions	Surgical evacuations	
	No.	No.	Row %
Total	5702	2934	51.5
Gestational age (week)			
13	218	156	71.6
14	812	560	69.0
15	1115	730	65.5
16	705	441	62.6
17	591	335	56.7
18	431	214	49.7
19	317	141	44.5
20	422	144	34.1
21	607	132	21.7
22	481	81	16.8
23	<4	0	0.0
Maternal age (years)			
15–19	736	383	52.0
20–24	1012	545	53.9
25–29	1271	621	48.9
30–34	1264	600	47.5
35–39	961	518	53.9
40–44	434	253	58.3
45–49	24	14	58.3
Previous deliveries			
Nulliparous	2970	1556	52.4
Only vaginal delivery with spontaneous delivery of the placenta	2120	1037	48.9
≥1 cesarean section	526	290	55.1
Manual removal placenta	86	51	59.3
Previous medical abortion			
No	5031	2609	51.9
≥1	671	325	48.4
Previous surgical abortion			
No	4699	2343	49.9
≥1	1003	591	58.9
Indication for termination			
Fetal	3067	1458	47.5
Health	352	177	50.3
Social	2234	1270	56.8
Unknown	49	29	59.2
Hospital			
Hosp1	31	5	16.1
Hosp2	281	111	39.5
Hosp3	456	222	48.7
Hosp4	591	313	53.0
Hosp5	208	41	19.7
Hosp6	372	86	23.1
Hosp7	202	120	59.4
Hosp8	171	120	70.2
Hosp9	512	341	66.6
Hosp10	395	189	47.8
Hosp11	112	83	74.1
Hosp12	341	188	55.1
Hosp13	241	125	51.9
Hosp14	351	237	67.5
Hosp15	253	174	68.8
Hosp16	255	103	40.4
Hosp17	63	26	41.3
Hosp18	96	53	55.2
Hosp19	228	100	43.9
Hosp20	249	147	59.0
Hosp21	294	150	51.0
Year of induction	*See* Fig. 1		

Table 2
Adjusted odds ratios of surgical evacuation following second-trimester medical abortions induced in Denmark in 2006–2017 according to gestational age, maternal age, history of reproductive events, indication for termination, year of induction, and hospital of induction.

	Adjusted odds ratio	95% confidence interval
Gestational age (week)		
13	1.29	(0.91;1.83)
14	1.16	(0.94;1.43)
15	1.00	Reference
16	0.82	(0.66;1.01)
17	0.63	(0.50;0.79)
18	0.46	(0.36;0.59)
19	0.36	(0.27;0.48)
20	0.17	(0.13;0.22)
21	0.09	(0.07;0.12)
22	0.07	(0.05;0.10)
23	–	–
Maternal age (year)		
15–19	0.77	(0.61;0.99)
20–24	0.97	(0.79;1.19)
25–29	1	Reference
30–34	0.92	(0.79;1.19)
35–39	1.02	(0.83;1.26)
40–44	1.01	(0.78;1.32)
45–49	1.06	(0.42;2.6)
Previous deliveries		
Nulliparous	1	Reference
Only vaginal delivery with spontaneous delivery of the placenta	0.79	(0.68;0.92)
≥1 cesarean section	1.13	(0.89;1.43)
Manual removal placenta	1.43	(0.86;2.39)
Previous medical abortion		
No	1	Reference
≥1	0.92	(0.76;1.12)
Previous surgical abortion		
No	1	Reference
≥1	1.18	(0.99;1.39)
Indication for termination		
Fetal	1	Reference
Health	1.10	(0.84;1.44)
Social	0.92	(0.79;1.08)
Unknown	0.93	(0.48;1.81)
Hospital		
Hosp1	0.05	(0.02;0.15)
Hosp2	0.36	(0.25;0.52)
Hosp3	0.61	(0.44;0.84)
Hosp4	0.64	(0.47;0.87)
Hosp5	0.15	(0.10;0.24)
Hosp6	0.15	(0.10;0.22)
Hosp7	0.99	(0.66;1.47)
Hosp8	1.70	(1.08;2.67)
Hosp9	2.38	(1.71;3.31)
Hosp10	0.57	(0.41;0.80)
Hosp11	1.35	(0.79;2.34)
Hosp12	0.68	(0.48;0.97)
Hosp13	0.91	(0.62;1.35)
Hosp14	1.00	Reference
Hosp15	1.90	(1.28;2.81)
Hosp16	0.39	(0.27;0.57)
Hosp17	0.35	(0.19;0.65)
Hosp18	0.68	(0.40;1.16)
Hosp19	0.63	(0.42;0.92)
Hosp20	0.97	(0.66;1.44)
Hosp21	0.93	(0.65;1.33)
Year of induction		
Effect of one-year-increase	0.82	(0.81;0.84)

The odds ratios were estimated by a multiple logistic regression model including gestational age, maternal age, previous deliveries, previous medical abortions, previous surgical abortions, indication for termination, year of induction, and hospital of induction.

found to be 2.5 (the *E*-value). Corresponding *E*-value for the association between time of induction and risk of surgical evacuation was 5.3.

Fig. 2 illustrates that most surgical evacuations occurred early after the initiation of medical induction.

Major surgery occurred in connection with ten abortions (0.2%), of which two abortions were induced due to maternal health issues. The ten events included one laparoscopy, three hysterotomies, five exploratory laparotomies, and one hysterectomy.

4. Discussion

This nationwide cohort study of 5702 second-trimester medical abortions showed a reduced risk of surgical evacuation with increasing gestational age, in women aged 15–19 years, and in women with a history of only vaginal deliveries with spontaneous delivery of the placenta. However, these risk factors could not explain the significant variation in risk of surgical evacuation among Danish hospitals and the decline in risk observed throughout time.

Few studies have tried to identify risk factors for surgical evacuation following medical termination of second-trimester pregnancies [3,4]. Contrary to these, we found gestational age to be the most significant risk factor for surgical evacuation [3,4]. It is known that later pregnancies are more sensitive to prostaglandins, and that the placenta is more adherent earlier in pregnancy, which can explain the observed association between gestational age and risk of surgical evacuation in the current study.

Consistent with the existing literature, we found a reduced risk among younger women [3,4]. A study concerning medical abortions induced in early first trimester shows that the induction-to-abortion interval, defined as the time from administration of prostaglandins to passage of products of conception, increases with increasing maternal age [14]. This may indicate a possible biological mechanism behind the advantage of being of younger age.

We found a reduced risk among women with a history of only vaginal deliveries with spontaneous delivery of placenta. The finding is inconsistent with prior studies showing no association between parity and risk of surgical evacuation following second-trimester medical abortions [3,4]. However, the inconsistency may be explained by the different categorization of the parity variable in the current study compared to the prior studies.

Our study clearly found year and hospital of induction to have a clinically significant influence on the risk of surgical evacuation. Even after adjusting for the identified risk factors, we still found a clinically profound decrease in risk of surgical evacuation throughout the study period and a sometimes-dramatic difference in risk between the different hospitals. From the beginning to the end of the study period, the proportion of surgical evacuation decreased from 64% to 26%, while the adjusted odds of surgical evacuation varied 44-fold between the department with the smallest and largest risk of surgical evacuation. We consider this difference in risk of surgical evacuation by time and site to be suggestive of an unwarranted variation, some surgical evacuations being medically unnecessary and potentially avoidable.

The decision to surgically evacuate, when suspecting treatment-demanding retained product of conception, is often based on a clinical estimate and not on objective measures, making the risk of surgical evacuation likely to be influenced by provider experience and tendencies/opinions. The quantitative bias analysis estimated that only a strong unmeasured risk factor, independent of the risk factors studied, could explain away the association

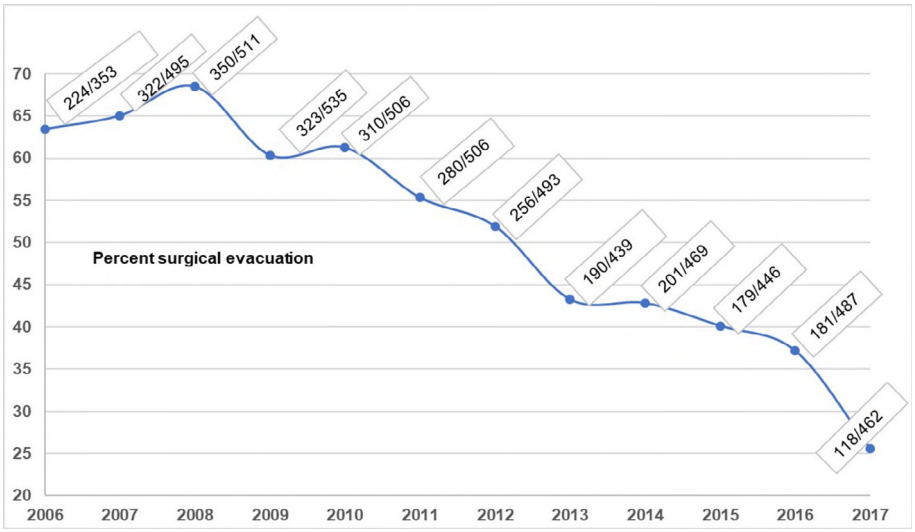

Fig. 1. Proportion of second-trimester medically induced abortions undergoing surgical evacuation in Denmark in 2006–2017 according to year of induction (annual number of surgical evacuations over annual number of total abortions).

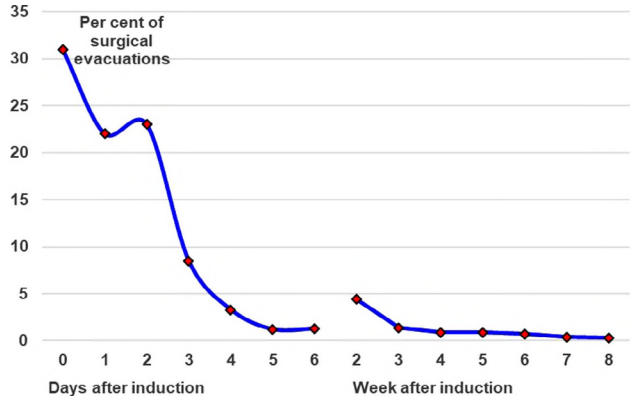

Fig. 2. Timing of surgical evacuation following medical induction of second-trimester abortion in Denmark in 2006–2017.

between risk of surgical evacuation and time/site of induction. We consider provider experience and provider tendencies/opinions to be the strongest unmeasured potential risk factor for surgical evacuation following second-trimester medical abortion. Provider experience in estimating the necessity of surgical evacuation due to retained product of conception is likely to have increased with time in Denmark, potentially explaining the decrease in risk of surgical evacuation observed throughout the study period. Furthermore, the acknowledgement of the benefits of avoiding surgical evacuation (provider tendencies/opinions) is also likely to have increased with time. This is backed up by observable declines in the proportion of first trimester missed abortions and incomplete spontaneous abortions treated with surgical evacuation in Denmark, the proportion of surgically evacuated missed abortions declining from 71% to 36% and that of incomplete spontaneous abortions from 32% to 17% during the period 2001–2018 [6].

Provider experience is also likely to differ among the Danish hospitals due to the difference in capacity (number and level of providers). Furthermore, although following the same clinical guideline, providers of some hospitals may tend to offer surgical evacuation more easily than providers from other hospitals due to different opinions on the matter, further contributing to the observed site variation in risk of surgical evacuation.

A maximum of ten out of 5702 second trimester terminations undergoing major surgery is a maximum of one in 570, which appears an acceptably low risk for such intervention, especially considering that only one of these events (the hysterectomy) had long-lasting reproductive consequences for the woman.

The obvious strengths of the study are the size of the cohort and the avoidance of selection bias due to the inclusion of all second-trimester medical abortions induced in Denmark during the study period. Furthermore, all abortions were followed for eight weeks from mifepristone administration with no abortion lost to follow-up.

The absence of information on the exact indication for surgical evacuation, that is the exact circumstances making the provider conclude the occurrence of treatment-demanding retained placenta, may be considered a limitation. The Danish National Patient Register does not systematically hold information on the indication for surgical evacuation. We consider this missing information as a minor limitation, since it does not compromise the finding of risk factors for surgical evacuation and their lack of ability to explain the variation by time and setting. However, had the assessment of the exact indications for surgical evacuation (excessive bleeding, visible incomplete placenta delivered, ultrasonographic findings, patient symptoms, patient request, combinations) been possible, it would have provided insight to the biological mechanisms of the associations observed between risk of surgical evacuation and the identified risk factors (gestational age/maternal age/previous deliveries).

The indication for pregnancy termination was maternal health in two out of the ten abortions that were followed by major surgery. This may suggest the potential importance of comorbidity in the risk of major surgery. Comorbidity information was not known, which could imply an overestimation of the risk of major surgery.

In conclusion, our study suggests an unwarranted variation in risk of surgical evacuation of second-trimester medical abortions in Denmark, which potentially could be explained by variation in provider experience and tendencies/opinions.

In Denmark, a maximum of 0.2% abortions were accompanied by major surgery, suggestive of a safe procedure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2020.04.017.

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