Risk factors for surgical intervention of early medical abortion

Amani Meaidi, MD, Sarah Friedrich, Phd, Thomas Alexander Gerds, Professor, Oejvind Lidegaard, Professor

PII: S0002-9378(19)30355-2

DOI: https://doi.org/10.1016/j.ajog.2019.02.014

Reference: YMOB 12556

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 29 October 2018

Revised Date: 16 January 2019

Accepted Date: 5 February 2019

Please cite this article as: Meaidi A, Friedrich S, Alexander Gerds T, Lidegaard O, Risk factors for surgical intervention of early medical abortion, *American Journal of Obstetrics and Gynecology* (2019), doi: https://doi.org/10.1016/j.ajog.2019.02.014.

12/01-2019

Risk factors for surgical intervention of early medical abortion

Amani Meaidi[1], *MD*

Sarah Friedrich[2], *Phd*

Thomas Alexander Gerds[3], *Professor*

Oejvind Lidegaard[1], *Professor*

[1]Department of Gynaecology, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

[2] Institute of Statistics, Ulm University, Helmholtzstraße 16, 89081 Ulm, Germany

[3] Department of Public Health, Section of Biostatistics, University of Copenhagen, Oester Farimagsgade 5, 1014 Copenhagen, Denmark

Disclosure statement

The authors report no conflict of interest.

Role of the funding source

Expenses were covered by Department of Gynecology, Rigshospitalet.

Paper presentation information

The findings were presented at the 13th annual conference of the International Federation of Professional Abortion and Contraception Associates (FIAPAC), Nantes, France, September 14th-15th, 2018.

Correspondence to

Amani Meaidi

Address: Blegdamsvej 9, 2100 Copenhagen, Denmark

E-mail: amani-meaidi@live.dk

Phone: +45 61 42 80 02

Word count

Abstract: 423, Main text: 2987

Condensation

A nationwide cohort study, identifying and quantifying gestational age, maternal age, and reproductive history as risk factors for surgical intervention of early medical abortion.

Short title

Risk factors for surgical intervention of early medical abortion

AJOG at Glance

A. Why was this study conducted?

Being non-invasive, early medical termination of unwanted pregnancy has increased worldwide access to induced abortion and improved safety of unsafe abortion. Thus, avoidance of secondary surgical intervention has important logistical and health-related implications worldwide. We therefore aimed to identify and quantify risk factors for surgical intervention of early first trimester medical abortions.

B. What are the key findings?

Gestational age, maternal age, previous deliveries, and history of induced abortion were all found to independently influence the risk of surgical intervention of early medically induced abortion.

C. What does the study add to what is already known?

This is the first nationwide study following a cohort of non-trial, real-life early medically induced abortions, identifying and quantifying risk factors for surgical intervention. The study both confirmed previous findings as well as assessed and quantified new risk factors.

Abstract

Background

By being non-invasive, medical termination of pregnancy has increased worldwide access to abortion and improved safety of unsafe abortion. However, secondary surgical intervention is the most frequent complication to medical abortion.

Objective

We aimed to identify and quantify risk factors for surgical intervention in women undergoing medically induced termination of pregnancy before nine completed weeks of gestation.

Study design

We conducted a nationwide cohort study, including all pregnancies terminated before 63 gestational days in women aged 15-49 years during the period 2005-2015. Induction regimen was 200 mg mifepristone followed 24-48 hours later by 0.8 mg vaginal misoprostol. All included pregnancies were followed up for eight weeks from mifepristone administration. Data were retrieved from national health registers. Multiple logistic regression provided adjusted odds ratios (ORs) of surgical intervention with 95% confidence intervals (CI). The discriminative ability of the risk factors in identifying surgical intervention was assessed by cross-validated area under the receiver operating characteristic curve (AUC).

Results

Of 86,437 early medical abortions, 5,320 (6.2%) underwent a surgical intervention within eight weeks after induction. The proportion of surgical interventions increased from 3.5% in the 5^{th}-6^{th} gestational week to 10.3% in week nine, OR 3.2 (95% CI 2.9–3.6). Compared to women aged 15-19 years, the risk of surgical intervention increased with increasing maternal age until the age of 30-34 years, OR 1.7 (95% CI 1.5–1.9), where after the risk decreased to an OR for age group 40-49 of 1.2 (95% CI 1.0–1.4). Compared to nulliparous women, a history of only vaginal deliveries with spontaneous delivery of placenta implied an OR of 1.1 (95% CI 1.0–1.2), women with a history of at least one cesarean section an OR of 1.5 (95% CI 1.3–1.6), and women having experienced a manual removal of placenta after a vaginal birth an OR of 2.0 (95% CI 1.7–2.4). Previous medically induced abortion decreased the risk of surgical intervention, OR 0.84 (95% CI 0.78–0.91), whereas previous early (before 56 days of gestation) surgically induced abortion implied a 53% (95% CI 1.4–1.7) increased risk of surgical intervention. Previous surgical abortion after 55 days of gestation increased the risk by

17% (95% CI 1.1–1.3). The AUC of the model including all quantified risk factors was 63% (95% CI 62-64%).

Conclusion

Gestational age, maternal age, previous deliveries, and history of medically and surgically induced abortions all had a significant influence on the risk of surgical intervention of early medical abortion. However, inclusion of all quantified risk factors still left most interventions unpredictable.

Key words

Cesarean section, complication, gestational age, induced abortion, maternal age, medical abortion, retained placenta, surgical abortion, uterine vacuum aspiration, vaginal delivery

Introduction

Medical termination of pregnancy before nine gestational weeks (early medical abortion) is a recognized procedure increasingly used worldwide.[1,2] Being noninvasive, early medical abortion improves safety and minimizes the infrastructural demands for the handling of terminations of pregnancies.[2]

Secondary surgical intervention is, however, the most frequent, clinically significant complication to early medical abortion and for those about five per cent experiencing this intervention, the otherwise obvious administrative, economical, and health-related advantages are challenged.

Despite the high and increasing use of early medical abortion worldwide, not much research has been made on possible risk factors for secondary surgical intervention.[2] Evidence on both acknowledged risk factors for surgical intervention, such as gestational age at time of the induction, as well as suggested risk factors, such as high maternal age, previous deliveries, and history of induced abortion, is sparse, inconsistent, and often based on outdated medical regimes.[3–8] To our knowledge, the predictive value of each of these recognized or possible risk factors has not been sufficiently evaluated.

Since 1997, early medical abortion with mifepristone and misoprostol has been available for all women with an unwanted pregnancy in Denmark. Apart from the first years after the introduction of the procedure, where 600 mg mifepristone was followed by 0.4 mg vaginal misoprostol, the typical regimen has been 200 mg mifepristone followed 24-48 hours later by 0.8 mg vaginally administrated misoprostol.[9,10] All legally induced abortions are registered in the Danish Register of Legally Induced Abortions ("abortion register").[11]

Considering the health and socioeconomic advantages of preventing the most frequent complication to one of the most commonly executed procedures within gynecology and the opportunities provided by the Danish registers, we followed a Danish nationwide cohort of early medical abortions with the aim of determining how gestational age, maternal age, previous deliveries, and history of induced abortion influence the risk of surgical intervention and to estimate the predictive performance of a model including these factors.

Methods

Early medical abortion in Denmark

Since 2005, early medical abortions have been induced at home, and the typical follow-up strategy to ensure completion of the abortion has been a halving of serum human chorionic gonadotropin (s-hCG) one week after the mifepristone administration.[10] If the follow-up s-hCG has been reduced by less than 50 %, women undergo transvaginal ultrasound examination. Surgical intervention has been offered when ultrasound has shown a persistent gestational sac or viable pregnancy. Otherwise, the decision to surgically intervene has been a clinical estimate made by the gynecologist on duty.[10]

Study population

We included all medical abortions induced in Denmark at a gestational age of less than 63 days during the period 2005 to 2015 among women aged 15-49 years, using the specific diagnostic and treatment codes by which medical abortions are registered in the abortion register (supplementary table 1).[11] The abortions were induced with 200 mg mifepristone followed 24-48 hours later by 0.8 mg vaginally administrated misoprostol.[10]

Study design

We followed all included pregnancies for eight weeks from mifepristone administration. Women receiving a surgical intervention (either uterine vacuum aspiration or a hysteroscopic excision of anticipated retained tissue) to complete the abortion are additionally given specific surgical codes at the time of surgical intervention in The Danish National Patient Register.[12] We defined a medical abortion as being surgically intervened, if one of these surgical codes was given during the eight weeks of follow-up (supplementary table 1).

Information on gestational and maternal age at first medical administration was extracted from the abortion register.[11] Data on history of induced abortion was achieved from the same register. We distinguished between previous medically induced abortion, previous surgically induced abortion induced before a gestational age of 56 days, and previous surgically induced abortion induced at a gestational age of ≥56 days (supplementary table 1).

The Danish Medical Birth Register and The Danish National Patient Register provided data on previous vaginal delivery, previous cesarean section, and previous manual removal of placenta (supplementary table 1).[12,13]

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

Statistical analysis

A multiple logistic regression model was used to analyze the association between the odds of surgical intervention and gestational age groups (5^{th}-6^{th}, 7^{th}, 8^{th}, and 9^{th} week), maternal age groups (15-19, 20-24, 25-29, 30-34, 35-39, 40-49 years), and reproductive history including previous medically induced abortions, previous surgically induced abortions, and previous deliveries. Calendar time was included in the model. Reported were adjusted odds ratios (OR) with 95 % confidence intervals (CI). To illustrate the effect of maternal age on a continuous age scale, a second multiple logistic regression analysis was performed, where instead of maternal age groups, a restricted cubic spline was used to model the effect of maternal age on the odds of surgical intervention. The number and placement of knots was chosen according to suggestions in Harrell, 2001.[14] The other variables in the model were unchanged. The result of the restricted cubic spline analysis was reported graphically as the risk of surgical intervention with corresponding pointwise 95% CIs according to maternal age, stratified by gestational age groups for given values of reproductive history and calendar time.

A subgroup analysis was made on first time medical abortions.

Linear trends of time since last induced abortion and of the number of previous induced abortions were analyzed in subgroups of women with previous surgical abortion and previous medical abortion, respectively, by entering the variables as numeric (one degree of freedom) in a multiple logistic regression model also including gestational age group, maternal age group, previous deliveries, and calendar time. Similarly, the effects of time since last delivery as well as number of deliveries were analyzed in subgroups of women with only previous vaginal deliveries with spontaneous delivery of placenta and women with at least one previous cesarean section, respectively.

To test the predictive value of gestational age, maternal age, previous deliveries, and history of induced abortion, the cohort of early medical abortions was divided into a training data set, including abortions induced in the years 2005-2012, and a validation data set with abortions induced in 2013-2015. The logistic regression model including gestational age groups, maternal age groups, previous deliveries, previous medical abortions, previous surgical abortions, and calendar time was then fitted on the training data set and tested on the validation data set. The same was done for the logistic regression model including maternal age modelled as a continuous variable with restricted cubic spline. Reported were the areas under the receiver operating characteristic (ROC) curves (AUCs) with

95% CIs. As a sensitivity analysis, we also randomly split the data into a training and validation data set, both of the same size as for the calendar year-based split.

All analyses were performed in R.[15]

Ethics approval

The study was approved by the Danish Data Protection Agency and the Danish Health Data Board. Ethics approval from the Danish National Committee on Health Research Ethics was not required due to the study being register-based.

Results

We identified 86,437 medical abortions induced before 63 days of gestation during the 11-year-long study period among women aged 15-49 years. Of these, 5,320 (6.2%) received a surgical intervention within 8 weeks from mifepristone administration, the majority being uterine vacuum aspirations and only 57 being hysteroscopic excisions of anticipated retained tissue.
Characteristics of the women at time of the medical induction are shown in table 1.

The proportion of surgical intervention increased from 3.5 % in abortions induced at a gestational age of 28-41 days to 10.3 % in abortions being 56-62 days at induction, OR 3.2 (95% CI 2.9-3.6; p<0.001; figure 1).

Compared to women aged 15-19 years, the risk of surgical intervention increased with increasing maternal age until the age group 30-34, OR 1.7 (1.5-1.9; p<0.001), here after the risk declined (figure 1). Figure 2 illustrates the absolute risk of surgical intervention for each maternal age according to the gestational age at time of the induction. Previous deliveries increased the risk of surgical intervention compared to nulliparous women (figure 1). The OR of surgical intervention for women with at least one previous cesarean section compared to women with a history of only vaginal deliveries (with spontaneous delivery of placenta) was 1.3 (1.2-1.5; p<0.001). Women who had experienced at least one manual removal of placenta had a doubled risk of surgical intervention compared to nulliparous women (figure 1).

While previous experience with medically induced abortion reduced the risk of surgical intervention, OR 0.84 (0.78-0.91; p<0.001), a history of surgically induced abortion increased the risk compared to women with no experience in surgical abortion. Women with a previous surgical abortion induced at <56 days of gestation had a higher risk of surgical intervention compared to women with a history of surgical abortion induced at or after 56 days of gestation (figure 1).

A subgroup analysis of only first time medical abortions showed no significant change in adjusted OR of surgical intervention associated to gestational age groups, maternal age groups, previous deliveries, and history of surgical abortions (supplementary figure 1).

A subgroup analysis of women having previously experienced a medically induced abortion showed that increasing number of previous medical abortions reduced the risk of surgical intervention (supplementary figure 2, p<0.001), while increasing time since last medical abortion reduced the protective effect of a previous medical abortion on the risk of surgical intervention (supplementary figure 2, p=0.010). The trend was opposite for women with a previous surgical abortion. In a subgroup

analysis of women having previously experienced a surgically induced abortion, increasing number of previous surgical abortions increased the risk of surgical intervention (supplementary figure 3, $p<0.001$), while increasing time since last surgical abortion reduced the negative impact of a previous surgical abortion on the risk of surgical intervention (supplementary figure 3, $p=0.003$).

A subgroup analysis of women with a history of only vaginal deliveries (with spontaneous delivery of placenta) showed no association between number of previous vaginal deliveries ($p=0.24$) or time since last delivery ($p=0.71$) and risk of surgical intervention (supplementary figure 4).

A similar subgroup analysis of women with at least one previous cesarean section showed no effect of time since last cesarean section ($p=0.54$). However, the odds of surgical intervention of an early medical abortion increased with increasing number of previous cesarean sections ($p=0.053$, supplementary figure 5).

Figure 3 shows the ROC curve for the prediction test performed on the calendar year-based division of the cohort. Characteristics of the cohort according to each data set are provided in supplementary table 2. The AUC was found to be 0.63 (95% CI: 0.62-0.64). The AUC was similar for the model including maternal age as a continuous variable modelled by a restricted cubic spline, AUC 0.63 (95% CI: 0.62-0.64). The AUC did not change significantly when calculated in sensitivity analyses where the division of the cohort in validation and training data set was done randomly.

Discussion

This nationwide cohort study of 86,437 early medical abortions showed gestational age, maternal age, previous deliveries, and history of induced abortion to influence the risk of surgical intervention of early medical abortions.

Complying with other studies on early medical abortions induced by 200 mg mifepristone followed 24-48 hours later by 0.8 mg vaginal misoprostol, we found a prevalence of surgical intervention of 6.2%.[16–20]

Of the variables studied, gestational age at time of the medical induction showed to be the most significant risk factor for surgical intervention, tripling the odds for medical abortions induced in the 9th gestational week compared to induction in week 5-6. Few studies have shown an increase in risk of surgical intervention with increasing gestational age.[16,17,21] A Cochrane review by Kulier et al., however, could not confirm this association.[4]

The restricted cubic spline modelling of maternal age showed a u-shaped association between maternal age and risk of surgical intervention, the risk peaking at its highest for women in their mid-thirties. Maternal age has previously been proposed as a risk factor for surgical intervention of early medical abortions.[5,7] To our knowledge, this is the first study allowing a detailed assessment of the association between maternal age and risk of surgical intervention also in very young women and for women aged 40-49 years, thereby revealing a u-shaped curve.

We found previous deliveries to be a risk factor for surgical intervention. While women with only previous vaginal deliveries with spontaneous delivery of placenta had a slight increase in risk of surgical intervention compared to nulliparous women, previous experience with cesarean section increased the risk by around 50 %, while previous necessity of a manual removal of placenta doubled the risk compared to nulliparous. Studies on early medical abortions induced by other medical regimes have suggested parity and cesarean section to be risk factors.[6,22,23] However, we did not find any study investigating the effect of previous placental retention on the risk of surgical intervention. Multiple studies have not been able to show an association between history of induced abortion and risk of surgical intervention.[5–7,22] However, none of these studies distinguished between the different types of induction. When stratifying into previous medically induced abortion, previous surgical abortion induced before or at/after 56 days of gestation, respectively, we found previous medical abortions to reduce the risk of surgical intervention, whereas previous surgical abortions increased the

risk, a history of surgical abortions induced before 56 days of gestation increasing the risk the most by around 50 %.

To our knowledge, this is the first nationwide study on risk factors for surgical intervention of early medical abortions. The obvious strengths of the study are the size of the included population, the lack of selection bias due to the inclusion of all early medical abortions induced in Denmark, as well as the full follow-up of all included abortions. A main limitation is the absence of information on the indication for each surgical intervention. This is due to the lack of systematic application of diagnosis codes on reason for surgical intervention in the everyday clinical practice, causing the information on indication to be missing or have inconsistent validity.

The decision to surgically intervene an early medical abortion is rarely based on medical necessity.[24] Ongoing pregnancy and health-threatening hemorrhage are not common observations in the course of early medical abortions and, therefore, rarely the indication for surgical intervention.[21,24] Often, the decision to surgically intervene is based on a clinical estimate that depends on the individual woman's symptoms, complains, and acceptability of the procedure as well as the physician's interpretation of the clinical and ultrasound findings. Thus, not knowing the exact indication for each surgical intervention made in the cohort limits the possibility to fully understand the causalities of the associations found. However, existing evidence as well as the subgroup analyses provided by this study contribute to the understanding of the nature of the associations. Ashok and colleagues observed an elimination of the association between gestational age and risk of surgical intervention by offering a second dose of misoprostol to women who did not achieve a complete abortion after the first dose, suggesting that increasing gestational age increase the risk of surgical intervention due to an increased risk of retained tissue.[8]

The finding of a u-shaped association between maternal age and risk of surgical intervention may indicate multicausality. Ashok and colleagues showed the induction-to-abortion interval, defined as the time from administration of prostaglandins to passage of products of conception, to increase with increasing maternal age.[8] On the other hand, Suhonen et al. found a negative correlation between age and pain evoked by medical abortion.[25] It is known that women's acceptability of the early medical abortion procedure influences the clinical decision to surgically intervene, low acceptability increasing the risk of surgical intervention.[24,26,27] Thus, when possible reasons exist for both increasing and decreasing risk of surgical intervention with increasing maternal age, the u-shaped association could be plausibly explained.

In a study of the association of ultrasonographic parameters of cesarean scar defect and outcome of early termination of pregnancy, Au and colleagues found that ultrasonographically visible cesarean scar defect was associated to an increased risk of surgical intervention of early medical abortion. [28] In the current study, we observed the trend of increased risk of surgical intervention with increasing number of previous cesarean sections, while no trend was observed for time since last cesarean section. These findings suggest and support that the association between previous cesarean section and risk of surgical intervention may be anatomical, e.g. related to scar formation.

Increasing number of previous surgical abortions was found to increase the risk of surgical intervention, a risk, however, decreasing over time. Increasing number of previous medical abortions had a protective effect, which also decreased by time. Women with a history of surgical abortions have experienced a different abortion procedure with less bleeding and pain experience. This may cause an expectation of less bleeding and pain during an early medical abortion, thereby less acceptability. If a woman is familiar with the sometimes extensive bleeding and pain accompanying a medical abortion due to prior experience, she may have higher acceptability. The impact of such previous experiences could mean less with time. We also found that women with a previous surgical abortion induced before a gestation of 56 days had a higher risk of surgical intervention compared to women with a history of surgical abortions induced at a gestation of 56 days or more. Since abortion providers in Denmark do not recommended surgical abortion for the termination of pregnancies with a gestational age of less than 56 days, most women with a history of such have gone against medical recommendations, possibly indicating a relatively low acceptability of medical abortions.

Although the study identified risk factors for surgical intervention of early medical abortions, the prediction performance of these risk factors was found to be low. We consider this finding to represent the above-mentioned complex, diverse, and multicausal nature of the indication for surgical intervention. Despite the low prediction performance, we believe that the knowledge of the existence of risk factors may contribute to a reduction of surgical interventions of early medical abortions.

Acknowledgement

The study was supported by Department of Gynecology, Copenhagen University Hospital, Rigshospitalet, Denmark.

References

1 World Health Organization, Department of Reproductive Health and Research. Safe abortion: technical and policy guidance for health systems. Geneva: *World Health Organization* 2012.

2 Singh S, Remez L, Sedgh G, Kwok L, Onda T. *Abortion Worldwide 2017: Uneven Progress and Unequal Access.* New York: *Guttmacher Institute* 2018.

3 Kahn JG, Becker BJ, MacIsaa L, Amory JK, Neuhaus J, Olkin I, Creinin MD. The efficacy of medical abortion: a meta-analysis. *Contraception* 2000; **61**:29–40.

4 Kulier R, Kapp N, Gülmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. *Cochrane Database of Systematic Reviews* 2011;**11**: Art.No.: CD002855.

5 Reeves MF, Monmaney JA, Creinin MD. Predictors of uterine evacuation following early medical abortion with mifepristone and misoprostol. *Contraception* 2016; **93**:119–125.

6 Chien LW, Liu WM, Tzeng CR, Au HK. Effect of previous live birth and prior route of delivery on the outcome of early medical abortion. *Obstet Gynecol* 2009;**113**:669–74.

7 Haimov-Kochman R, Arbel R, Sciaky-Tamir Y, Brzezinski A, Laufer N, Yagel S. Risk factors for unsuccessful medical abortion with mifepristone and misoprostol. *Acta Obstet Gynecol Scand* 2007;**86**:462–6.

8 Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Factors affecting the outcome of early medical abortion: a review of 4132 consecutive cases. *BJOG* 2002;**109**:12819.

9 Knudsen UB. First trimester abortion with mifepristone and vaginal misoprostol. *Contraception* 2001;**63**:247-250.

10 Danish National Clinical Guideline on Medical Abortion, 1. Trimester. Updated 2014. https://static1.squarespace.com/static/5467abcce4b056d72594db79/t/548e08cee4b06f8a5b8130d7/1418594510349/14-11-29+Ab+med+guide+14.pdf [Last accessed, 8th of October 2018].

11 Tølbøll Blenstrup L, Knudsen LB. Danish registers on aspects of reproduction. *Scand J Public Health* 2011 Jul 1;**39**:79–82.

12 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;**39**:30—3.

13 Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull.* 1998;**45**:320–323.

14 Harrell FE. Regression modeling strategies, with applications to linear models, survival analysis and logistic regression. London: *Springer*, 2001.

15 R Core Team. R: A language and environment for statistical computing. *RFoundation for statistical Computing*. Vienna, Austria, 2017; URL https://www.R-project.org/.

16 Von Hertzen H, Piaggio G, Wojdyla D, et al. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. *Br J Obstet Gynaecol* 2009;**116**:381–9.

17 Tang OS, Chan CC, Ng EH, Lee SW, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. *Hum Reprod* 2003;**18**:2315–8.

18 Shannon C, Wiebe E, Jacot F, et al. Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. *Br J Obstet Gynaecol* 2006;**113**:621–8.

19 Chawdhary R, Rana A, Pradhan N. Mifepristone plus vaginal misoprostol vs vaginal misoprostol alone for medical abortion in gestation 63 days or less in Nepalese women: a quasi-randomized controlled trial. *J Obstet Gynaecol Res* 2009;**35**:78–85.

20 Middleton T, Schaff E, Fielding SL, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005;**72**:328–32.

21 Ashok PW, Penney GC, Flett GM, Templeton A. An effective regimen for early medical abortion: a report of 2000 consecutive cases. *Human Reproduction* 1998;**13**:2962–5.

22 Bartley J, Tong S, Everington D, Baird DT. Parity is a major determinant of success rate in medical abortion: a retrospective analysis of 3161 consecutive cases of early medical abortion treated with reduced doses of mifepristone and vaginal gemeprost. *Contraception* 2000;**62**:297–303.

23 Dehlendorf, et al. Medication abortion failure in women with and without previous cesarean delivery. Contraception. 2015;92:463-8.

24 Allen RH, Westhoff C, De Nonno L, Fielding SL, Schaff EA. Curettage after mifepristone-induced abortion: Frequency, timing, and indications. *Obstet Gynecol* 2001;**98**:101–6.

25 Suhonen S, Tikka M, Kivinen S, Kauppila T. Pain during medical abortion: predicting factors from gynecologic history and medical staff evaluation of severity. *Contraception* 2011;83:357-361.

26 Spitz I, Bardin W, Benton L, Robbins A. Early pregnancy termination with mifepristone in the United States. *N Engl J Med* 1998;**338**:1241– 6.

27 Winikoff B, Sivin I, Coyaji K, Cabezas E, Bilian X, Sujuan G, et al. Safety, efficacy, and acceptability of medical abortion in China, Cuba, and India: A comparative trial of mifepristone-misoprostol versus surgical abortion. *Am J Obstet Gynecol* 1997;**176**:431–7.

28 Au H, Liu C, Tzeng C, Chien L. Association between ultrasonographic parameters of Cesarean scar defect and outcome of early termination of pregnancy. *Ultrasound Obstet Gynecol* 2016;**47**: 506-510.

Figure Legends:

Figure 1: Adjusted ORs of surgical intervention according to gestational age, maternal age, and previous reproductive events among women undergoing an early medical abortion. The adjusted ORs were derived from a multiple logistic regression model including gestational age groups, maternal age groups, previous deliveries, previous medical abortions, previous surgical abortions, and calendar time.

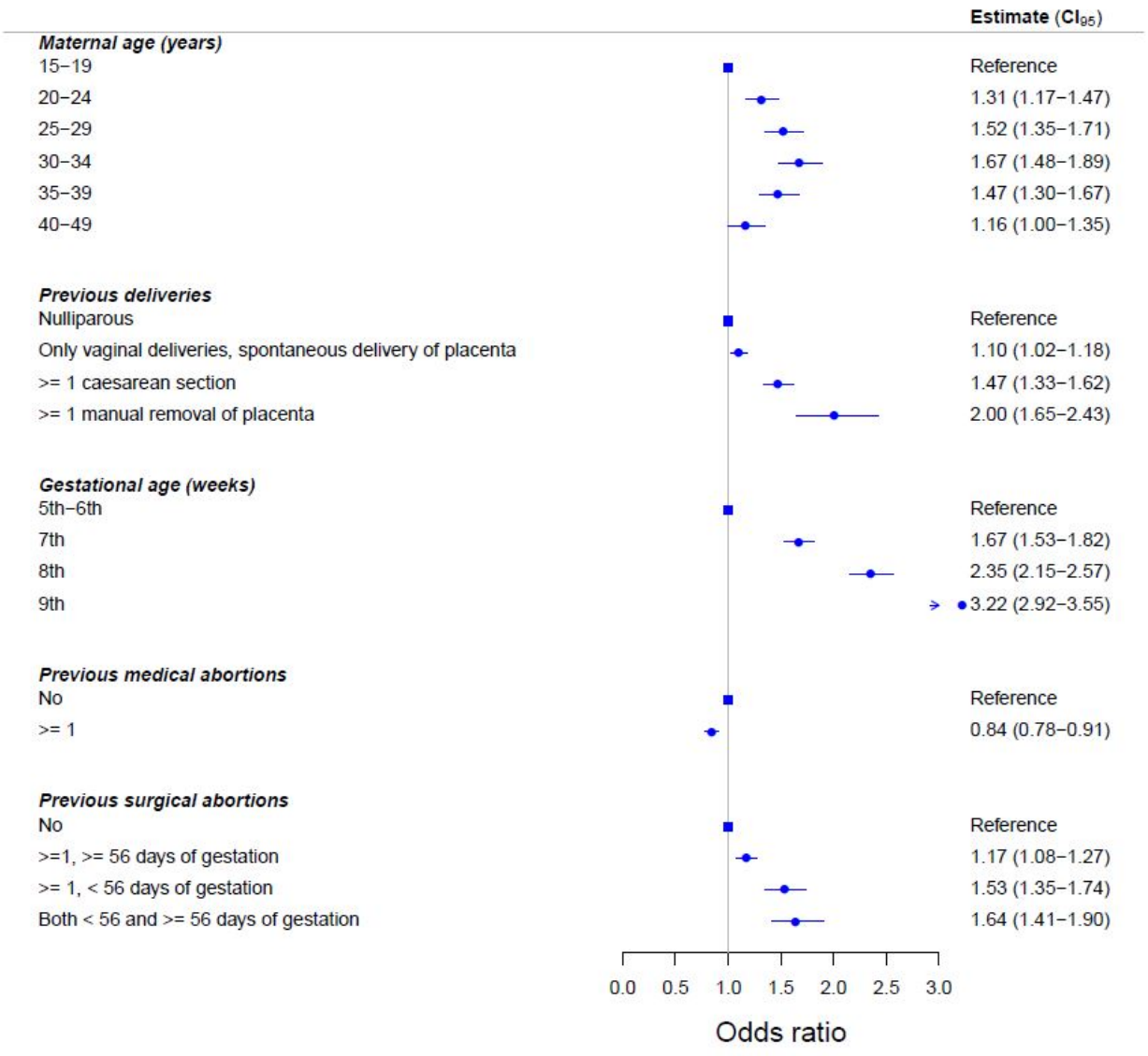
Figure 2: Absolute risks of surgical intervention according to maternal age, stratified by gestational age, and adjusted for no previous deliveries, no history of induced abortions, and the calendar year of 2012. The assessment of the risks was based on a multiple logistic regression model including maternal age modelled as a continuous variable via a restricted cubic spline, gestational age groups, previous deliveries, previous medical abortions, previous surgical abortions, and calendar time.

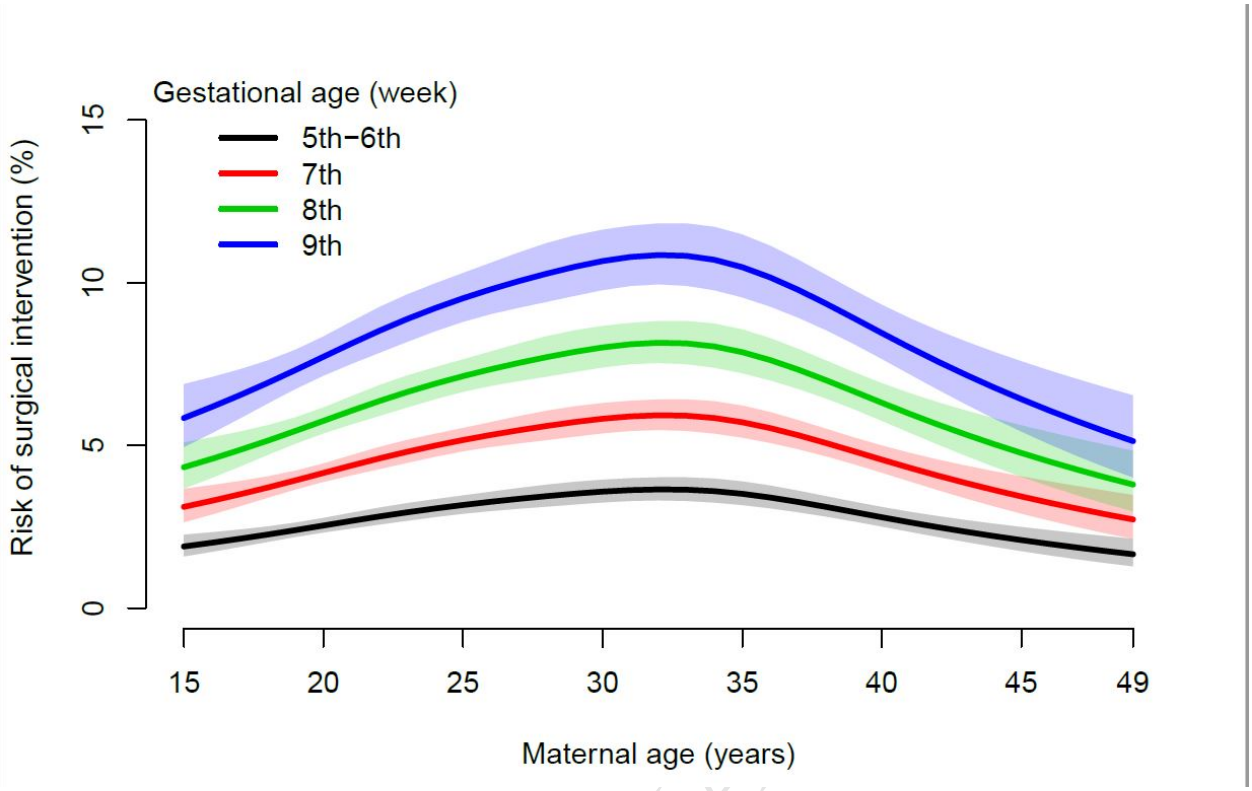
Figure 3: The receiver operating characteristic (ROC) curve of the prediction performance of the multiple logistic regression model including gestational age groups, maternal age groups, previous deliveries, previous medical abortions, previous surgical abortions, and calendar time. The training data set, on which the multiple regression model was fitted, consisted of the abortions induced during the period 2005-2012, while the validation data set, on which the model was tested, consisted of abortions induced during 2013-2015.

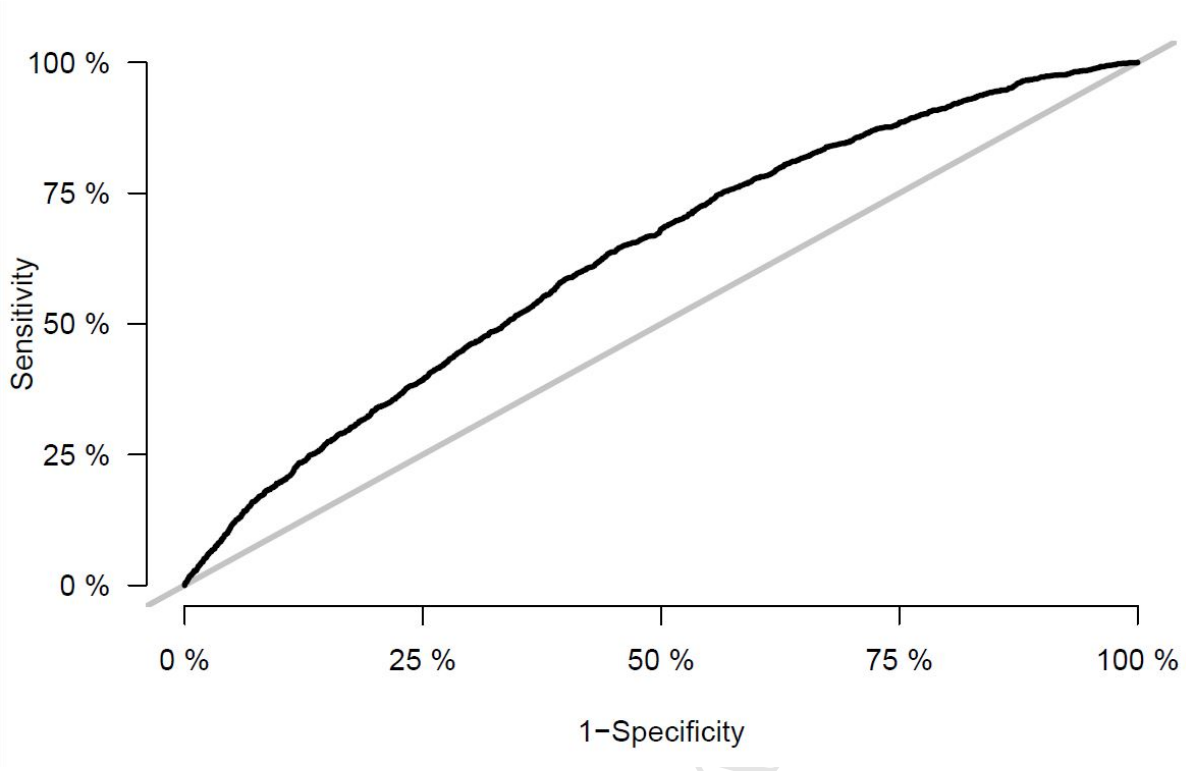
Table 1: Maternal age and reproductive history according to gestational age in women undergoing an early medical abortion.

Gestational age in days **Gestational age in weeks**	**28-41** **5-6th**	**42-48** **7th**	**49-55** **8th**	**56-62** **9th**	**28-62** **5-9th**
Number of abortions	21969	32632	22050	9786	86437
Per cent distribution	25·4	37·8	25·5	11·3	100
Maternal age (years)					
15-19	2594 (11·8)	4058 (12·4)	2827 (12·8)	1344 (13·7)	10823 (12·5)
20-24	5405 (24·6)	7903 (24·2)	5364 (24·3)	2454 (25·1)	21126 (24·4)
25-29	4546 (20·7)	6589 (20·2)	4411 (20·0)	1973 (20·2)	17519 (20·3)
30-34	4091 (18·6)	6140 (18·8)	4218 (19·1)	1787 (18·3)	16236 (18·8)
35-39	3457 (15·7)	5267 (16·1)	3623 (16·4)	1579 (16·1)	13926 (16·1)
40-49	1876 (8·5)	2675 (8·2)	1607 (7·3)	649 (6·6)	6807 (7·9)
Previous deliveries					
Nulliparous	10374 (47·2)	16210 (49·7)	11170 (50·7)	5041 (51·5)	42795 (49·5)
Only vaginal deliveries, spontaneous delivery of placenta	8913 (40·6)	12810 (39·3)	8566 (38·8)	3728 (38·1)	34017 (39·4)
≥1 caesarean section	2365 (10·8)	3167 (9·7)	2031 (9·2)	893 (9·1)	8456 (9·8)
≥1 manual removal of placenta	317 (1·4)	445 (1·4)	283 (1·3)	124 (1·3)	1169 (1·4)
Previous medical abortions					
No	16988 (77·3)	26311 (80·6)	17799 (80·7)	7723 (78·9)	68821 (79·6)
≥1	4981 (22·7)	6321 (19·4)	4251 (19·3)	2063 (21·1)	17616 (20·4)
Previous surgical abortions					
No	17689 (80·5)	26359 (80·8)	17858 (81·0)	7831 (80·0)	69737 (80·7)
≥1, <56 days of gestation	1049 (4·8)	1311 (4·0)	803 (3·6)	299 (3·1)	3462 (4·0)
≥1, ≥56 days of gestation	2611 (11·9)	4173 (12·8)	2884 (13·1)	1424 (14·6)	11092 (12·8)
Both <56 and ≥56 days of gestation	620 (2·8)	789 (2·4)	505 (2·3)	232 (2·4)	2146 (2·5)

Column percentages are shown in ().







Supplementary material

Supplementary table 1: Data sources as well as diagnosis and treatment codes used to identify variables of interest

Variable	Data source	Codes from The International Classification of Diseases and Related Health Problems, 10th Revision, The Nordic Medico-Statistical Committee Classification of Surgical Procedures, and The Danish Classification System for Non-Surgical Procedures
Medically induced abortion, study unit	The Register of Legally Induced Abortions*	DO04/DO06 + BKHD40 + BKHD41
Previous medically induced abortion	The Register of Legally Induced Abortions	DO04-06 + BKHD40/BKHD44 + BKHD41/BKHD45
Previous surgically induced abortion	The Register of Legally Induced Abortions	DO04-06 + KLCH03/KLCH00
Previous delivery	The Danish Medical Birth Register**	Each observation in the data source consists of one delivery
Cesarean section	The Danish National Patient Register***	KMCA00-96
Manual removal of placenta	The Danish National Patient Register	KMBA30
Surgical intervention subsequent to a medically induced abortion	The Danish National Patient Register	KMBA 00, KMBA03, KLCH00, KLCH03, KLCH13, KLCB98, KLCB25, KULC02

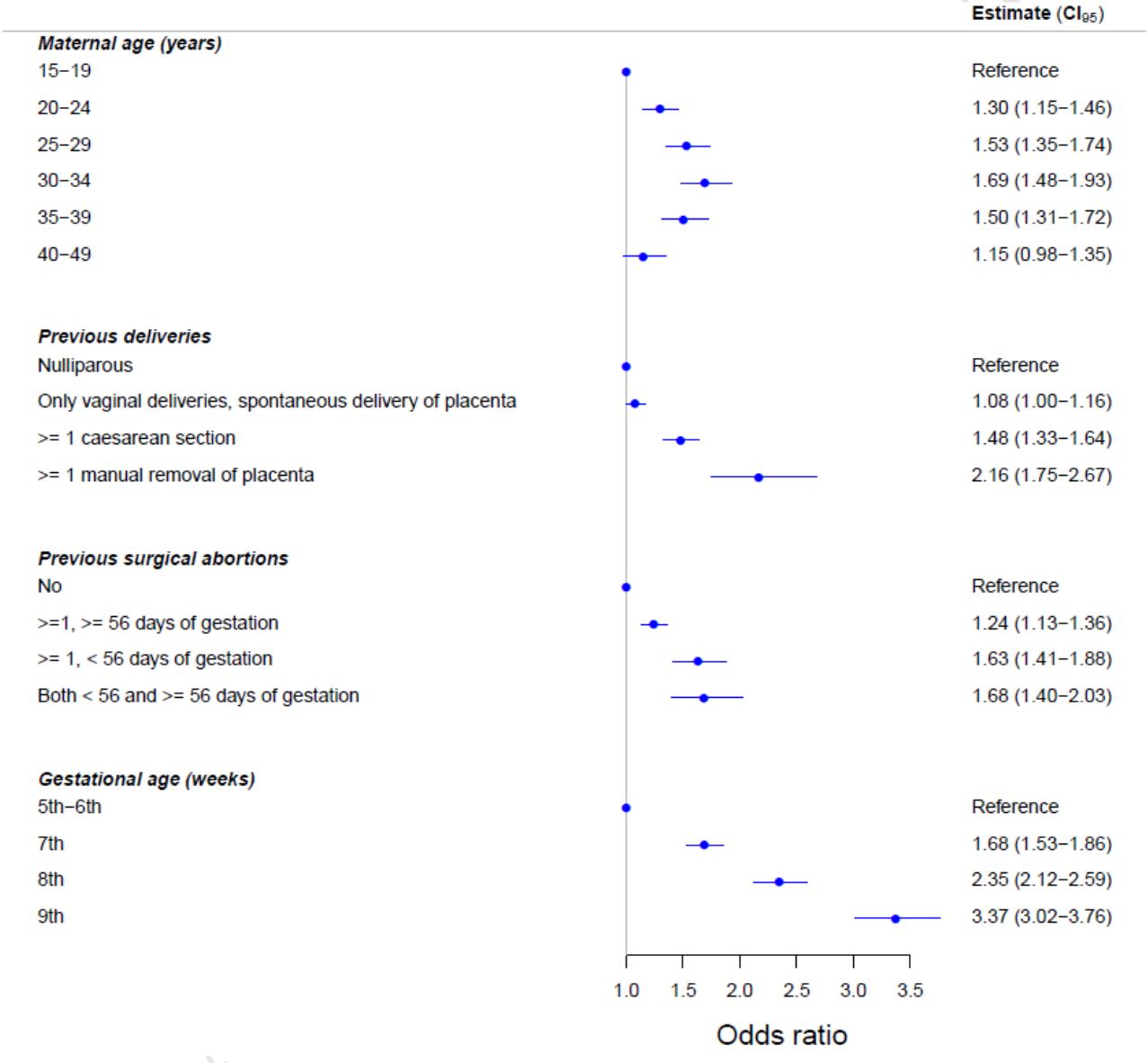
*11
**13
***12

Supplementary table 2: Gestational age, maternal age, and reproductive history according to training and validation data set for the primary prediction performance test. The training and validation data set are based on a calendar-time division of the original cohort.

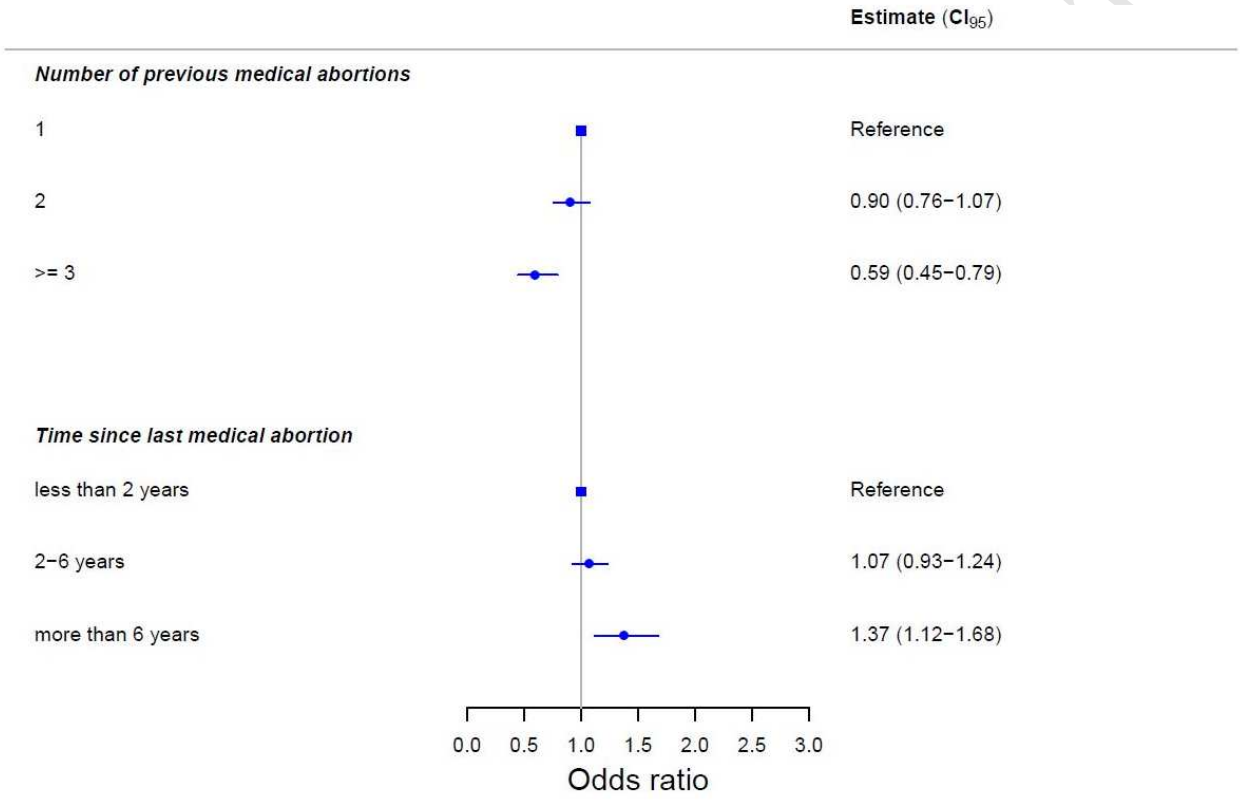
Variable	Training set n (%)	Validation set n (%)	Total n (%)
Abortions	57,259 (66·2)	29,178 (33·8)	86,437 (100)
Gestational age			
5th-6th week	12835 (22·4)	9134 (31·3)	21969 (25·4)
7th week	21818 (38·1)	10814 (37·1)	32632 (37·8)
8th week	15591 (27·2)	6459 (22·1)	22050 (25·5)
9th week	7015 (12·3)	2771 (9·5)	9786 (11·3)
Maternal age			
15-19	7329 (12·8)	3494 (12·0)	10823 (12·5)
20-24	13315 (23·3)	7811 (26·8)	21126 (24·4)
25-29	11000 (19·2)	6519 (22·3)	17519 (20·3)
30-34	11205 (19·6)	5031 (17·2)	16236 (18·8)
35-39	9807 (17·1)	4119 (14·1)	13926 (16·1)
40-49	4603 (8·0)	2204 (7·6)	6807 (7·9)
Previous deliveries			
Nulliparous	28272 (49·4)	14523 (49·8)	42795 (49·5)
Only vaginal deliveries, spontaneous delivery of placenta	22727 (39·7)	11290 (38·7)	34017 (39·4)
Caesarean section (≥1)	5565 (9·7)	2891 (9·9)	8456 (9·8)
Manual removal of placenta (≥1)	695 (1·2)	474 (1·6)	1169 (1·4)
Previous medical abortions			
No	47110 (82·3)	21711 (74·4)	68821 (79·6)
≥1	10149 (17·7)	7467 (25·6)	17616 (20·4)
Previous surgical abortions			
No	46216 (80·7)	23521 (80·6)	69737 (80·7)
≥1, <56 days of gestation	2359 (4·1)	1103 (3·8)	3462 (4·0)
≥1, ≥56 days of gestation	7319 (12·8)	3773 (12·9)	11092 (12·8)
Both <56 and ≥56 days of gestation	1365 (2·4)	781 (2·7)	2146 (2·5)

Figure legends:

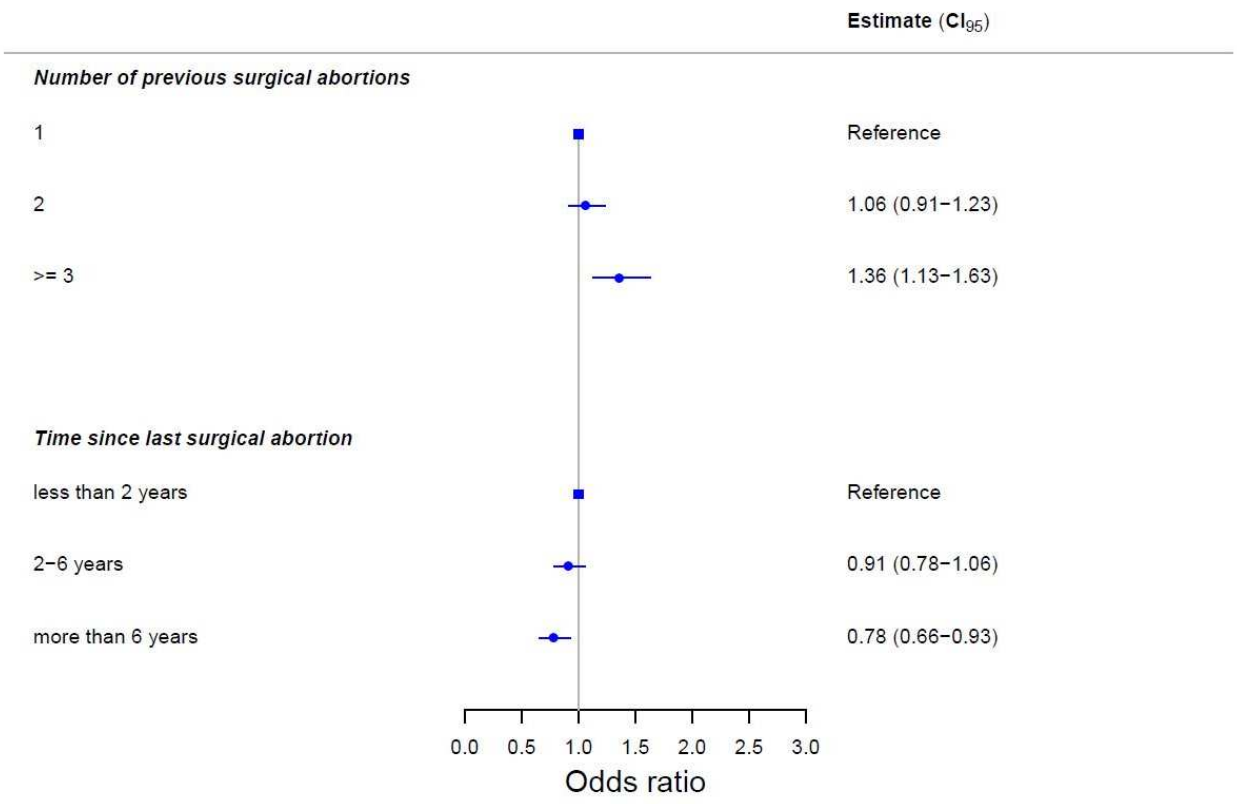
Supplementary figure 1: Adjusted ORs and corresponding 95 % CIs of surgical intervention according to maternal age, gestational age, and previous reproductive events in women with no previous experience with medically induced abortions. The ORs were estimated by a multiple logistic regression model including maternal age groups, gestational age groups, previous deliveries, previous surgical abortions, and calendar time.



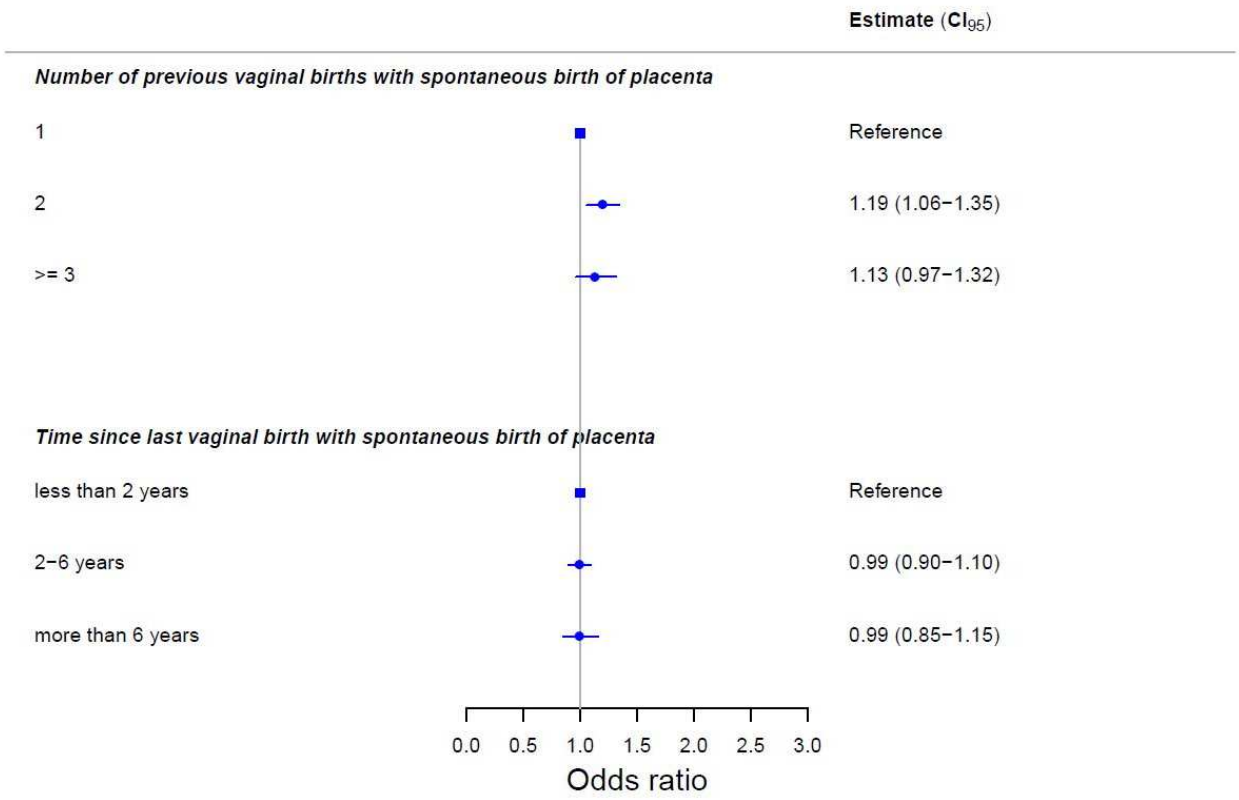
Supplementary figure 2: Adjusted ORs and corresponding 95 % CIs of surgical intervention according to number of previous medical abortions and time since last medical abortion in women having experienced at least one previous medical abortion. The ORs were estimated by a multiple logistic regression model including number of previous medical abortions, time since last medical abortion, maternal age groups, gestational age groups, previous deliveries, previous surgical abortions, and calendar time.



Supplementary figure 3: Adjusted ORs and corresponding 95 % CIs of surgical intervention according to number of previous surgical abortions and time since last surgical abortion in women having experienced at least one previous surgical abortion. The ORs were estimated by a multiple logistic regression model including number of previous surgical abortions, time since last surgical abortion, maternal age groups, gestational age groups, previous deliveries, previous medical abortions, and calendar time.



Supplementary figure 4: Adjusted ORs and corresponding 95 % CIs of surgical intervention according to number of previous vaginal deliveries (with spontaneous delivery of placenta) and time since last vaginal delivery (with spontaneous delivery of placenta) in women having experienced only previous vaginal deliveries (with spontaneous delivery of placenta). The ORs were estimated by a multiple logistic regression model including number of previous vaginal deliveries (with spontaneous delivery of placenta), time since last previous vaginal delivery (with spontaneous delivery of placenta), maternal age groups, gestational age groups, previous medical abortions, previous surgical abortions, and calendar time.



Supplementary figure 5: Adjusted ORs and corresponding 95 % CIs of surgical intervention according to number of previous caesarean sections and time since last caesarean section in women having experienced at least one previous caesarean section. The ORs were estimated by a multiple logistic regression model including number of previous caesarean sections, time since last caesarean section, maternal age groups, gestational age groups, previous medical abortions, previous surgical abortions, and calendar time.