Reproductive outcomes following induced abortion: a national register based cohort study in Scotland

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000911
Article Type:	Research
Date Submitted by the Author:	20-Jan-2012
Complete List of Authors:	Bhattacharya, Siladitya; University of Aberdeen, Institute of Applied Health Sciences Lowit, Alison; University of Aberdeen, Institute of Applied Health Sciences Bhattacharya, Sohinee; University of Aberdeen, Public Health Raja, Edwin Amalraj; University of Aberdeen, Medical Statistics, Dept. of Public Health Lee, Amanda; University of Aberdeen, Medical Statistics, Dept. of Public Health Mahmood, Tahir; Forth Park Hospital, Obstetrics and Gynaecology Templeton, Allan; University of Aberdeen, Institute of Applied Health Sciences
Primary Subject Heading:	Reproductive medicine, obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS, PERINATOLOGY, REPRODUCTIVE MEDICINE

Reproductive outcomes following induced abortion: a national register based cohort study in Scotland

Siladitya Bhattacharya[1], Alison Lowit[1] Sohinee Bhattacharya[1*], Amalraj Raja[1], Amanda J Lee[1], Tahir Mahmood[2], Allan Templeton[1]

[1]Division of Applied Health Sciences, University of Aberdeen

[2]Forth Park Hospital, Kirkcaldy

*Corresponding author

All correspondence to:

Dr Sohinee Bhattacharya

University of Aberdeen

Aberdeen Maternity Hospital

Cornhill Road

Aberdeen AB25 2ZD

Tel: +44 1224 554672

Fax: +44 1224 559948

Email: sohinee.bhattacharya@abdn.ac.uk

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: The Chief Scientist Office Scotland funded the study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Contribution, (v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, (vi) licence any third party to do any or all of the above.

Funding for this research was obtained from a research grant from the Chief Scientist's Office in Scotland (CZG_2_403) but the funding body played no role in the design, analysis or interpretation of the results.

Ethical Approval: Approval was obtained from the Privacy Advisory Committee of the Information and Services Division of the National Health Service in Scotland

Abstract

Objective: To investigate reproductive outcomes in women following induced abortion (IA).

Design: Retrospective cohort study

Setting: Hospital admissions between 1981 and 2007 in Scotland.

Participants: Data were extracted on all women who had an IA, a miscarriage or a live birth from the Scottish Morbidity Records. A total of 120,033, 457,477 and 47,355 women with a documented second pregnancy following an IA, livebirth and miscarriage respectively were identified.

Outcomes: Obstetric and perinatal outcomes, especially preterm delivery in a second ongoing pregnancy following an IA were compared with those in primigravidae, as well as those who had a miscarriage or live birth in their first pregnancy. Outcomes after surgical and medical termination as well as after one or more consecutive IAs were compared.

Results: IA in a first pregnancy increased the risk of spontaneous preterm birth compared to that in primigravidae [Adjusted relative risk (Adj. RR) 1.37, 95% Confidence Interval (CI) 1.32, 1.42] or women with an initial live birth [Adj. RR 1.66, 95% CI 1.58-1.74], but not in comparison with women with a previous miscarriage [Adj. RR 0.85, 95% CI 0.79-0.91].

Surgical abortion increased the risk of spontaneous preterm birth compared to medical abortion [Adj. RR 1.25, 95% CI 1.07-1.45)]. The adjusted relative risks (95% CI) for spontaneous preterm delivery following two, three and four consecutive IAs were 0.94 (0.81-1.10), 1.06 (0.76-1.47) and 0.92 (0.53-1.61) respectively.

Conclusion: The risk of preterm birth after induced abortion is lower than that after miscarriage but higher than that in a first pregnancy or after a previous live birth. This risk is not increased further in women who undergo two or more consecutive induced abortions. Surgical abortion appears to be associated with an increased risk of spontaneous preterm birth in comparison with medical termination of pregnancy.

Background

Many women start their reproductive careers with an abortion in their first pregnancy. In 2011, 12,826 abortions were performed in Scotland (accessed 3rd November 2011) with the highest rates in women aged 16-19 years [1]. What is

not yet entirely clear is the effect these abortions may have on subsequent childbearing. Following the legalisation of abortion in 1967, initial research on the effects of an induced abortion on subsequent pregnancies showed no evidence of an increased risk of miscarriage, preterm delivery or low birth weight [2,3]. Much of the work in the subject has been hampered by methodological limitations. Randomised controlled studies are not feasible in this context and researchers have looked to observational studies. Many of the published studies have been limited by small sample sizes, self-reported outcomes and the inability to adjust for many potential confounders. A recent review [4] reported that six out of twelve relevant studies found an association between induced abortion and preterm birth, as well placenta praevia. More recently a number of large studies found no increased risk of placenta praevia, but reported an association with preterm [5-7] and very preterm delivery [8-10]. The clinical implications of this are profound as preterm delivery, with its associated problems, remains one of the most significant challenges in obstetrics.

Over a quarter of induced abortions in Scotland in 2005 were repeat procedures[1]. While the reproductive sequelae of repeat abortions are unclear, the available literature suggests that the risk of preterm delivery is increased by multiple abortions [5,6,8,11].

Changes in the technique of induced abortion have to be taken into account when assessing their impact on future reproduction. In 1992, 83.6% of terminations were carried out surgically, falling to 60.6% in 1998 and 40.7% in 2006, with the remainder being carried out medically [1]. A number of studies [12-14] have compared these methods in terms of safety, efficacy and short term complications, but data on subsequent reproductive outcomes is scant. A recent study [15] found no difference in reproductive outcomes (ectopic, miscarriage and preterm delivery) following medically and surgically induced abortions, but was unable to adjust for known confounders such as smoking.

In view of the high current rates of induced abortion, it is essential that women, and those involved in their care, are aware of the reproductive consequences of induced abortion.

The Scottish Morbidity Record (SMR) system in Scotland covers a national population and has captured data on medical and surgical abortions for many years. Over 99.3% of abortions in Scotland are carried out in NHS premises and are recorded in the SMR system. As these data are based on clinical records, any potential bias created by underreporting will be removed. The availability of this large national dataset provides an ideal opportunity to link records on abortion (SMR01) with maternity records (SMR02) in order to explore the risk of preterm delivery and other maternal and perinatal outcomes in women following one or more episodes of induced abortion. The data would also allow a meaningful comparison of outcomes following alternative forms of induced abortion (i.e. medical versus surgical).

The primary aim of this study was to investigate reproductive outcomes in women following induced abortion. In particular we wished to answer the following research questions: 1) Is an induced abortion *in a first pregnancy* associated with spontaneous preterm birth or other adverse obstetric or perinatal outcomes in the second pregnancy? 2) Is an induced abortion performed *after an initial singleton livebirth* associated with spontaneous preterm birth or adverse obstetric or perinatal outcomes in the next pregnancy? 3) Do any of these associations differ by method of induced abortion (i.e. surgical versus medical)? 4) Is the risk of adverse obstetric or perinatal outcomes associated with increasing number of terminations?

Methods

A retrospective cohort study design was used on routinely collected anonymised data extracted from the ISD database. Approval was obtained from the Privacy

Advisory Committee of the Information and Statistics Division (ISD) of the National Health Service, Scotland.

To answer research question 1, data were extracted from the ISD databases (SMR01 and 02) on women aged 15-55 years who had an induced abortion (IA), a miscarriage, or a livebirth in their first pregnancy between 1981 and 2007 which was followed by a second pregnancy event. Reproductive outcomes in the subsequent pregnancy of women who had an IA in their first pregnancy (exposed cohort) were compared with those in two unexposed comparison groups: women in their second pregnancy after a miscarriage in their first pregnancy (Group 1) and women in their second pregnancy after a livebirth in their first pregnancy (Group 2). In addition to these two unexposed cohorts, obstetric and perinatal outcomes in a pregnancy following IA in a first pregnancy (exposed cohort) were also compared with first pregnancy outcomes in women in Group 2 i.e. a primigravid cohort.

To explore outcomes following early pregnancy loss after an initial livebirth (research question 2), data were extracted on all women (15-55 years of age) who had an induced abortion, a miscarriage, or a livebirth, in their second pregnancy (following a livebirth in their first pregnancy) between 1981 and 2007 from the ISD databases (SMR01 and 02) and followed up to identify a third pregnancy event. Reproductive, obstetric and perinatal outcomes in women who had an IA after a singleton term first pregnancy (exposed group) were compared with those in two unexposed groups: (1) women in their third pregnancy following a singleton term delivery in the first pregnancy and a miscarriage in the second pregnancy and (2) women in their third pregnancy following two singleton term deliveries.

Women treated by different methods of induced abortion (surgical or medical) in a first pregnancy were compared in terms of reproductive, obstetric and perinatal outcomes (research question 3). Finally, to answer research question 4,

reproductive and perinatal outcomes were compared between groups of women who had 1, 2, 3 and 4 previous consecutive induced abortions.

Data extraction

The following variables were identified by matching SMR01 and SMR02 datasets between the years 1981 and 2007.

Demographic data: Age at pregnancy events, smoking, and social class (assessed using Carstairs category of deprivation). Induced abortion data: estimated gestation and method of termination (medical or surgical or both). Reproductive outcomes: miscarriage, abortion, livebirth, ectopic and stillbirth. Obstetric and perinatal outcomes: pre-eclampsia, placenta praevia, placental abruption, preterm delivery, very preterm delivery, low birth weight and the mode of delivery. Spontaneous delivery rates were calculated after excluding women who had induced labour and elective (planned) caesarean section.

Socioeconomic status was assessed using the Carstairs categories of social deprivation [16] which was divided into quintiles for analysis.

Power calculation

Given the number of sub-groups in the analysis coupled with multiple outcomes, a global sample size calculation was not feasible. Preliminary enquiries with ISD suggested that we could identify at least 260,000 terminations (1981-2007), of which 30% (n=69,000) were estimated to have had a subsequent livebirth and 25.5% (n=66,223) were induced abortions in a first pregnancy.

Using a 1:1 ratio of women with induced abortions in a first pregnancy (exposed cohort 1) and unexposed women, we anticipated having over 90% power, at the two-sided 5% significance level, to detect a difference of 0.5% or more in the chances of a preterm birth (an odds ratio of 1.09) assuming that the prevalence of livebirths in the unexposed group was 6%.

Statistical analysis

In the absence of an ideal comparison group for women with a prior abortion, we used 3 unexposed cohorts which could increase the chance of false positive

associations (type I error). To minimise this, we used a stringent p-value of ≤0.01 to denote statistical significance throughout the statistical analyses. Statistically significant relative risks are shown in bold in the relevant tables. Stata version 11 was used throughout the analysis.

Descriptive statistics were used to summarise reproductive outcomes, maternal & perinatal outcomes and potential predictor variables (age, smoking, Carstairs quintiles) between the various exposure groups for each research question in turn. Appropriate univariate analyses [chi square test for comparing categorical variables across exposure groups, t-test (two group comparison) and ANOVA (multiple group comparison) to compare mean differences in age at pregnancy event] across exposure groups were performed.

A generalised linear model was used with Poisson family and robust variance estimator to ascertain the relationship between exposure (first pregnancy induced abortion) and various reproductive outcomes (still birth, miscarriage, ectopic and induced abortion), maternal and perinatal outcomes (pre-eclampsia, placenta-previa, abruption placenta) after adjusting for potential confounders (maternal age, year of delivery, smoking, Carstairs category at relevant pregnancy & interpregnancy interval between exposed and relevant pregnancy). For the outcome of induction of labour, pre-eclampsia, placenta previa and placental abruption were also entered into the model. Similarly, the model pertaining to the outcome low birth weight was also adjusted for gestational age.

As smoking data were not routinely collected before 1992, and rarely collected for women having an induced abortion or miscarriage, smoking status was missing for a high percentage of women. This sometimes led to non-convergence of the statistical models. Therefore, a sensitivity analysis was carried out by re-running all of the multivariate models following exclusion of the smoking variable to determine if the overall effect sizes remained of similar magnitude. This was found to be so.

Results

Demographic characteristics of primigravida, as well as women who had an abortion, livebirth or a miscarriage in their first pregnancy are shown in Table 1. Women with a previous induced abortion were younger and more socially deprived in comparison with women with a livebirth or miscarriage in their first pregnancy. The interpregnancy interval was longest for the abortion group and shortest in women with an initial miscarriage.

Reproductive outcomes following IA, miscarriage and livebirth are shown in Table 2. IA in the first pregnancy increased the risk of having an induced abortion, miscarriage or ectopic pregnancy in the second pregnancy as compared with an initial livebirth. Compared to those who had an initial miscarriage, women who had an IA in their first pregnancy were less likely to have a subsequent still birth, miscarriage or ectopic pregnancy but more likely to have a second induced abortion.

Perinatal outcomes in the next ongoing pregnancy following IA are compared with those in primigravidae and women with an initial a livebirth or miscarriage in Table 2. Compared with women having a previous livebirth, an IA put women at higher risk of pre-eclampsia, abruptio placenta, induction of labour, spontaneous preterm and very preterm delivery (<34 weeks) and delivery of a low birth weight baby (<2500 g).

In comparison with women with a previous miscarriage, a history of IA decreased women's chances of developing pre-eclampsia and spontaneous preterm and very preterm delivery. Risks of pre-eclampsia, placental abruption, delivery of a low birth weight baby and spontaneous preterm and very preterm birth were significantly higher following IA than in primigravid women. The risk of pre-eclampsia in women with a previous IA was higher that in primigravid women but lower than in women with a previous miscarriage (Table 2).

The demographic characteristics of women who had a livebirth in a first pregnancy and then went on to have induced abortion, livebirth or a miscarriage

in their second pregnancy are shown in Table 3. Women with an induced abortion in their second pregnancy were younger, belonged to a more deprived social group and were more likely to be smokers than women who had a livebirth or miscarriage in their second pregnancy.

Table 4 shows that reproductive outcomes following an induced abortion, livebirth or miscarriage in the second pregnancy in a cohort of women who had a livebirth in their first pregnancy. The risk of miscarriage in a third pregnancy was reduced in women who had either an IA or a livebirth in a second pregnancy, but the risks of another induced abortion were higher than in women with a previous miscarriage.

Compared to women with two previous livebirths, women with a livebirth followed by an IA were more likely to have pre-eclampsia, placenta praevia, induced labour and spontaneous preterm or very preterm birth (Table 4). They were also more likely to deliver low birthweight babies (<2500g). Women with an IA in a second pregnancy were not at any higher risk of perinatal complications in comparison with women with a previous miscarriage with the exception of an increased risk of having a low birthweight baby.

In records where the method of IA was clearly recorded, 52,560 women were noted to have had surgical and 16,702, medical abortions. As Table 5 shows, reproductive outcomes were comparable in the two groups except for a lower risk of a second induced abortion following surgical termination of pregnancy. The adjusted relative risk of miscarriage, ectopic pregnancy, placenta praevia and spontaneous preterm delivery (<37 weeks) were higher after surgical termination of pregnancy.

Table 6 summarises the perinatal outcomes in subsequent pregnancies following one or more consecutive IAs. The adjusted relative risks of having a low birth weight baby, an induction of labour, preterm birth or very preterm birth were not significantly increased by two, three or four consecutive IAs versus one IA.

Discussion

Principal findings

Our results indicate that women who undergo induced abortion in the first pregnancy have an increased risk of spontaneous preterm labour in comparison with primigravid women or those with a previous livebirth. This risk is lower than that faced by women with a previous miscarriage.

A livebirth prior to an IA does not appear to reduce perinatal risks in women who remain at higher risk of spontaneous preterm birth than primigravidae. Surgical termination appears to be associated with a higher chance of spontaneous preterm (but not very preterm) birth than medical IA. There does not appear to be a statistically significant dose dependent effect of IA on future adverse perinatal outcomes. Women with three or four consecutive induced abortions were not at significantly higher risk of spontaneous preterm birth in comparison with women who have had one termination of pregnancy.

Strengths

To our knowledge this is the largest population based study of reproductive outcomes following an induced abortion. In addressing this question we have been able to compare outcomes after medical and surgical abortion and explore the dose dependent effect of abortion on future preterm delivery. An added strength is use of national data and the ability to discriminate between spontaneous and overall preterm birth as an outcome.

Our analysis is based on data collected over a number of years. In acknowledgement of changes in clinical practice during this time, we have adjusted for year of pregnancy. The choice of an appropriate comparison group to women with a history of induced abortion is problematic. Women who become pregnant after having an induced abortion in a first pregnancy are gravida 2 and para 0. It is impossible to control for both gravidity and parity unless the unexposed cohort have had a prior pregnancy which did not lead to a delivery. Other comparison groups can be either women in their first ongoing pregnancies (gravidity 1 parity 0), or in their second ongoing pregnancies after a previous

delivery (gravidity 2 parity 1). We feel that our strategy comparing the exposed cohort to all three of the above groups adds validity to our results.

Limitations

The main limitations of this study stem from unrecorded and missing data in relation to certain potential confounding factors within the dataset. For example, smoking data were only available for 50% of women; data on body mass index were unavailable, while data on gestational age at termination were missing in the majority of cases. The actual method of termination (medical versus surgical) was unrecorded in around 25% of all cases while a large number of women appeared to have both medical as well as surgical treatment. Parity number was less reliable in the early years of data collection. This may reflect problems with coding and could potentially affect the quality of our results. In addition the analysis of such a large population based dataset has the capacity to produce statistically significant differences which may or may not be clinically relevant, although this has been minimised by our use of a 1% significance level throughout.

Comparison with previous studies

The association between induced abortion and preterm birth found in this study is consistent with previously published work [17]. Two recent meta-analyses suggest that women who have had an IA are at higher risk of preterm birth in subsequent pregnancies [18,19]. Our study shows that after adjustment, women with a previous abortion have an increased chance of a subsequent spontaneous preterm birth and very pre-term birth compared with primigravidae or those who have had a previous livebirth, but at lower risk compared to women who have had a previous miscarriage. Women who had a livebirth before an induced abortion are also more likely to have a spontaneous preterm birth compared to women with two previous livebirths.

Our results did not suggest an increased risk of miscarriage after an induced abortion which is in keeping with [4] review of literature. In contrast, Sun and

colleagues [20] demonstrated an association between surgical abortion and miscarriage in a subsequent pregnancy. Literature on the association between IA and miscarriage or ectopic pregnancy is sparse and conflicting. Thus our findings of increase in ectopic rates after IA compared to women with a previous livebirth merit further study. The higher odds of having a second induced abortion following induced abortion in a first pregnancy as shown in our study have been reported elsewhere [21-23].

Available data are suggestive of an association between IA and placenta previa [24, 25], but no association with abruptio placenta [26,27]. We found that women in their second pregnancy after an initial induced abortion in the first were at higher odds of placental abruption but women in their third pregnancy after an induced abortion in their second pregnancy had higher odds of placenta previa but not abruptio placenta. Published evidence supports a decreased risk of pre-eclampsia after an IA [28,29]. Our results suggest that the risk of pre-eclampsia following IA is higher than that faced by primigravid and parous women but lower than after a previous miscarriage.

Since the introduction of medical abortion there has been much speculation about the rival merits of medical and surgical techniques in terms of future reproductive outcomes. Analysis of Danish data has failed to demonstrate a difference in key outcomes such as preterm birth between medical and surgical abortion [15] in a study which was unable to identify spontaneous versus induced preterm birth. Our results based on the analysis of a larger cohort and with the ability to identify spontaneous preterm births show a clear association with surgical abortion. As we were unable to adjust for gestational age, we cannot rule out the possibility that surgical abortions may have been performed at a more advanced stage of pregnancy requiring a greater degree of cervical dilatation – thus leading to future preterm labour.

A dose dependent relationship between the number of IAs and future preterm birth has been shown in a number of previous studies [17]. The results of our analysis do not support this. Given our inability to adjust for a number of potential confounders, this needs to be investigated further.

Meaning of the results

These results confirm previously noted association between abortion and the risk of preterm birth, but highlight the importance of interpreting the data in context. Thus the increased risk of spontaneous preterm birth is marked in comparison with two of our unexposed cohorts, but reduced in comparison with that in women with a previous early pregnancy loss. This emphasises the continuum between miscarriage and spontaneous preterm birth and underlines the fact that the risk of the latter after IA is lower than after what is widely regarded as a common complication of early pregnancy. These data should be useful in a clinical context whilst counselling women contemplating pregnancy or attending an early pregnancy clinic.

Conclusions

The risk of spontaneous preterm birth following an induced abortion is higher in comparison with women in their first pregnancy or after a previous livebirth, but lower than in women with a previous miscarriage. A successful pregnancy leading to a livebirth prior to an induced abortion does not appear to ameliorate this risk while more than one abortion does not appear to increase it. Medical abortion appears to be associated with a lower risk of spontaneous preterm birth in comparison with surgical termination of pregnancy. The results of this study should help provide women as well as health professionals with accurate information to inform clinical decision making and service delivery models for termination of pregnancy.

Contribution to authorship

AT conceived the idea for the study. SB was the Principal Investigator. He designed the study along with SohB, AT, ALee and TM, led the funding

application, managed the project, interpreted the results and wrote the first draft of the paper. ALo cleaned the data and performed some of the initial analyses. SohB co-wrote the funding application, facilitated data manipulation, interpreted the results and helped to draft the paper. EAR performed the statistical analysis and interpreted the results with input from ALee. All authors commented on, and contributed to the final draft of the paper.

Acknowledgements

We thank staff at ISD Scotland for extraction of data from the Scottish Morbidity Records Database and Margery Heath for secretarial assistance.

Funding

The Chief Scientist Office Scotland funded the study. The views expressed are those of the authors and not the funding body.

References

1. Information and Statistics Division (ISD) of the National Health Service, Scotland. http://www.isdscotland.org/isd/CCC_FirstPage.jsp-.
2. Atrash HK, Hogue CJ. The effect of pregnancy termination on future reproduction. *Baillieres Clin Obstet Gynaecol* 1990; Jun;4(2):391-405.
3. Hogue CJ. Impact of abortion on subsequent fecundity. *Clinics in Obstetrics & Gynaecology* 1986;13(1):95,96-103.
4. Thorp JM, Hartmann KE, Shadigian E. Long-term physical and psychological health consequences of induced abortion: review of the evidence. *Obstet Gynecol* Survey 2002; 58;1(67):79.
5. Ancel PY, Lelong N, Papiernik E, et al. History of induced abortion as a risk factor for preterm birth in European countries: results from the EUROPOP survey. *Hum Reprod* 2004;19(3):734-40.
6. Zhou W, Sorensen HT, Olsen J. Induced abortion and subsequent pregnancy duration. *Obstet Gynecol* 1999; Dec;94(6):948-53.
7. Raatikainen K, Heiskanen N, Heinonen S. Induced abortion: not an independent risk factor for pregnancy outcome, but a challenge for health counseling. *Ann Epidemiol* 2006; Aug;16(8):587-92.
8. Moreau C, Kaminski M, Ancel PY, Bouyer J, Escande B, Thiriez G, et al. Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study. *BJOG* 2005; Apr;112(4):430-7.
9. Zhou W, Nielsen GL, Larsen H, Olsen J. Induced abortion and placenta complications in the subsequent pregnancy. *Acta Obstet Gynecol Scand* 2001; Dec;80(12):1115-20.
10. Johnson IG, Mueller BA, Daling JR. The relationship of placenta previa and history of induced abortion. *Int J Gynecol & Obstet* 2003;81(2):191-8.
11. Henriet L, Kaminski M. Impact of induced abortions on subsequent pregnancy outcome: the 1995 French national perinatal survey. *BJOG* 2001; Oct;108(10):1036-42.

12. Henshaw RC, Naji SA, Russsell IT, Templeton A. A comparison of medical abortion (using mifepristone and gemeprost) with surgical vacuum aspiration: efficacy and early medical sequelae. *Human Reproduction* 1994;9(11):2167,2168-71.
13. Ashok PW, Kidd A, Flett GM, Fitzmaurice A, Graham W, Templeton A. A randomized comparison of medical abortion and surgical vacuum aspiration at 10-13 weeks gestation. *Human Reproduction* 2002;17(1):92,93-8.
14. Rorbye C, Norgaard M, Nilas L. Medical versus surgical abortion efficacy, complications and leave of absence compared in a partly randomized study. *Contraception 2004* 2004;70(5):393,394-9.
15. Virk J, Zhang J, Olsen J. Medical abortion and the risk of subsequent adverse pregnancy outcomes. *N Engl J Med* 2007; Aug 16;357(7):648-53.
16. Carstairs V, Morris R. *Deprivation and Health in Scotland* 1991
17. Lowit A, Bhattacharya S. Obstetric performance following an induced abortion. *Best Practice & Research - Clinical Obstetrics & Gynaecology* 2010;24(5):667,668-82.
18. Shah PS, Zao J. Induced termination of pregnancy and low birth weight and preterm birth: a systemic review and meta-analysis. *BJOG* 2009;116:1425-42.
19. Swingle HM, Colaizy TT, Zimmerman MB, et al. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analysis. *J Reprod Med* 2009;54:95-108.
20. Sun Y, Che Y, Ershang G, et al. Induced abortion and risk of subsequent miscarriage. *Int J Epidemiol* 2003; 32;(449):454.
21. Heikinheimo O, Gissler M, Suhonen S. Age, parity, history of abortion and contraceptive choices affect the risk of repeat abortions. *Contraception 2008* 2008;149,150-4.

22. Prager SW, Steinauer JE, Foster DF, Darney PD, Drey EA. Risk factors for repeat elective abortion. *American Journal of Obstetrics & Gynecology* 2007;197:e1-575,576-e6.
23. Rowlands S. More than one abortion. *Joural Fam Plann Reprod Health Care* 2007;33(3):155,156-8.
24. Ananth CV, Smulian JC, Vintzileos AM. The effect of placenta previa on neonatal mortality: a population-based study in the United States, 1989 through 1997. *Am J Obstet Gynecol* 2003; May;188(5):1299-304.
25. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta abruption in an Asian population. *Reproductive Sciences* 2007;14(1):59-65.
26. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta previa in an Asian population. *Int J Gynecol & Obstet* 2007;97:26-30.
27. Zhu QX, Gao ES, Chen AM, et al. Mifepristone-induced abortion and placenta complications in subsequent pregnancy. *Hum Reprod* 2009;24(2):315-9.
28. Eras JL, Saftlas AF, Triche E, et al. Abortion and its effect on risk of pre-eclampsia and transient hypertension. *Epidemiology* 2000;11:36-43.
29. Trogstad L, Magnus P, Skjaerven R, et al. Previous abortions and risk of pre-eclampsia. *Int J Epidemiology* 2008;37:1333-40.

TABLE 1: Demographic characteristics at first pregnancy of women who had induced abortion, livebirth or miscarriage in their first pregnancy

		Outcome in first pregnancy				
		Induced abortion N=120,033	**Live birth N=457,477**	**p-value**	**Miscarriage N=47,355**	**p-value**
Mean Age (SD)		24.68 (7.56)	24.89 (5.11)	<0.001	26.26 (6.13)	<0.001
Carstairs Category [1,2]	1	17265 (17.1)	79705 (18.0)	<0.001	8403 (18.8)	<0.001
	2	18538 (18.3)	81661 (18.4)		8206 (18.4)	
	3	19530 (19.3)	84559 (19.1)		8794 (19.7)	
	4	21135 (20.9)	92504 (20.9)		9426 (21.1)	
	5	24615 (24.4)	105313 (23.7)		9788 (21.9)	
Smoking status[2]	Never	1014 (42.3)	112744 (48.4)	<0.001	4892 (39.8)	<0.001
	Current	676 (28.2)	72182 (31.0)		2044 (16.6)	
	Former	85 (3.5)	22140 (9.5)		533 (4.3)	
	Not known	622 (26.0)	26088 (11.2)		4818 (39.2)	
	Total	2397	233154		12287	
	Missing	117636 (98.0)	224323 (49.0)		35068 (74.1)	
Interpregnancy interval in Weeks	Median (IQR)	165 (78, 321)	139 (95, 213)	<0.001	65 (47, 104)	<0.001

Values are n (%) unless otherwise specified

[1] Carstairs categories 1 = least deprived, 5 = most deprived

[2] Percentage based on available information for each group

TABLE 2: Reproductive and perinatal outcomes following induced abortion, miscarriage or live birth in first pregnancy

Outcome of 2nd pregnancy	**Outcome in First pregnancy**				**Crude and Adjusted (Adj.) Relative Risk (99% CI)** [1]		
	Induced abortion N=120033	**Live birth N=457477**	**Miscarriage N=47355**		**Induced abortion vs Live birth**	**Induced abortion vs Miscarriage**	
Live birth	67336 (56.1)	355674 (77.7)	36479 (77.0)		Crude 0.72 (0.71, 0.73) Adj. 0.74 (0.73, 0.74)	Crude 0.72 (0.72, 0.73) Adj. 0.69 (0.69, 0.70)	
Still birth	409 (0.34)	1406 (0.31)	247 (0.52)		Crude 1.11 (0.96, 1.28) Adj. 1.06 (0.91, 1.24)	Crude 0.65 (0.53, 0.80) Adj. **0.58(0.46, 0.74)**	
Miscarriage	7965 (6.6)	30669 (6.7)	6197 (13.1)		Crude 0.99 (0.96, 1.02) Adj. **1.05(1.01, 1.08)**	Crude 0.51 (0.49, 0.53) Adj. **0.56(0.54, 0.59)**	
Ectopic	1115 (0.9)	2939 (0.6)	499 (1.1)		Crude 1.45 (1.32, 1.58) Adj. **1.36(1.23, 1.50)**	Crude 0.88 (0.77, 1.01) Adj. **0.83(0.71, 0.97)**	
Induced abortion	43208 (36.0)	66789 (14.6)	3933 (8.3)		Crude 2.47 (2.43, 2.50) Adj. **2.30(2.27, 2.33)**	Crude 4.33 (4.16, 4.51) Adj. **4.64(4.44, 4.85)**	
Outcomes in ongoing pregnancies	**N=67745**	**N=357080**	**N=36726**	**Primigravida N=457477**			**Induced abortion vs Primigravida**
Pre-eclampsia	1583 (2.3)	2982 (0.8)	922 (2.5)	8649 (1.9)	Crude 2.80 (2.58, 3.03) Adj. **2.42 (2.21, 2.65)**	Crude 0.93 (0.84, 1.03) Adj. **0.83 (0.73, 0.94)**	Crude 1.24 (1.15, 1.32) Adj. **1.26 (1.17, 1.35)**
Placentaprevia	385 (0.6)	1919 (0.5)	289 (0.8)	2042 (0.5)	Crude 1.06 (0.92, 1.22) Adj. 1.09 (0.93, 1.28)	Crude 0.72 (0.59, 0.88) Adj. 0.79 (0.62, 1.01)	Crude 1.27 (1.10, 1.47) Adj. 1.05 (0.91, 1.22)
Abruptio placenta	339 (0.5)	1197 (0.3)	173 (0.5)	1770 (0.4)	Crude 1.49 (1.27, 1.75) Adj. **1.49 (1.25, 1.77)**	Crude 1.06 (0.84, 1.35) Adj. 1.00 (0.76, 1.32)	Crude 1.30 (1.11, 1.51) Adj. **1.28 (1.10, 1.50)**
Induction of labour[2]	18044 (26.6)	69482 (19.5)	10347 (28.2)	120080 (26.3)	Crude 1.37 (1.34, 1.39) Adj. **1.33 (1.30, 1.35)**	Crude 0.95 (0.92, 0.97) Adj. 0.98 (0.95, 1.01)	Crude 1.01 (1.00, 1.03) Adj. 1.00 (0.99, 1.02)
Low birth weight <2500g[3]	5385 (8.0)	16309 (4.6)	3101 (8.5)	28735 (6.3)	Crude 1.74 (1.67, 1.81) Adj. **1.24 (1.17, 1.31)**	Crude 0.94 (0.89, 1.00) Adj. 0.96 (0.90, 1.03)	Crude 1.27 (1.22, 1.31) Adj. **1.08 (1.04, 1.13)**
Outcomes in spontaneous births	**N= 45656**	**N=255220**	**N=23751**	**N=318217**			
Spontaneous preterm birth <37 weeks	4224 (9.3)	13453 (5.3)	2376 (10.0)	21891 (6.9)	Crude 1.76 (1.68, 1.83) Adj. **1.66 (1.58, 1.74)**	Crude 0.92 (0.86, 0.97) Adj. **0.85 (0.79, 0.91)**	Crude 1.35 (1.29, 1.40) Adj. **1.37 (1.32, 1.42)**
Spontaneous very preterm birth <34 weeks	1512 (3.3)	3994 (1.6)	865 (3.6)	7154 (2.3)	Crude 2.12 (1.96, 2.29) Adj. **2.00 (1.83, 2.18)**	Crude 0.90 (0.82, 1.01) Adj. **0.86 (0.76, 0.98)**	Crude 1.47 (1.37, 1.58) Adj. **1.52 (1.41, 1.63)**

Values are n (%) unless otherwise specified

[1] Adjusted for maternal age, year of delivery, Carstairs at first pregnancy & interpregnancy interval.

[2] Further adjusted for pre-eclampsia, placenta previa & abruptio placenta.

[3] Low birth weight also adjusted for gestational age.

TABLE 3: Demographic characteristics of women who had induced abortion, livebirth or miscarriage after an initial livebirth

		Outcome in second pregnancy following an initial livebirth				
		Induced abortion N=30527	**Live birth N=125855**	**p-value**	**Miscarriage N=22404**	**p-value**
Mean Age (SD)		26.04 (5.85)	26.15 (4.68)	<0.001	28.41 (5.42)	0.001
Carstairs Category[1,2]	1	3523 (12.8)	20264 (16.5)	<0.001	4498 (20.9)	<0.001
	2	4304 (15.6)	21985 (17.9)		4079 (18.9)	
	3	5186 (18.8)	23425 (19.0)		4312 (20.0)	
	4	6243 (22.6)	25979 (21.1)		4447 (20.6)	
	5	8370 (30.3)	31395 (25.5)		4235 (19.6)	
Smoking status[2]	Never	393 (39.7)	32464 (48.5)	<0.001	3165 (46.1)	0.001
	Current	313 (31.6)	20658 (30.9)		1169 (17.0)	
	Former	43 (4.3)	5359 (8.0)		282 (4.1)	
	Not known	241 (24.3)	8482 (12.7)		2243 (32.7)	
	Total	990	66963		6859	
	Missing	29537 96.8)	58892 (46.8)		15545 (69.4)	
Interpregnancy interval	Median(IQR)	108 (61, 209)	152 (96, 256)	<0.001	60 (48, 87)	<0.001

Values are n (%) unless otherwise specified

[1] Carstairs categories 1 = least deprived, 5 = most deprived

[2] Percentage based on available information for each group

TABLE 4: Reproductive and perinatal outcomes in women who had induced abortion, livebirth or miscarriage following a livebirth in the first pregnancy

Outcome of 3rd pregnancy	Outcome of second pregnancy			Crude and Adjusted (Adj.) Relative Risk (99% CI) [1]	
	Induced abortion N=30527	Live birth N=125855	Miscarriage N=22404	Induced abortion vs Live birth	Induced abortion vs Miscarriage
Live birth	18562 (60.8)	85014 (67.5)	17745 (79.2)	Crude 0.90 (0.89, 0.91) Adj. 0.88 (0.87, 0.89)	Crude 0.77 (0.76, 0.78) Adj. 0.77 (0.76, 0.78)
Still birth	84 (0.3)	426 (0.3)	69 (0.3)	Crude 0.81 (0.60, 1.11) Adj. 0.76 (0.55, 1.06)	Crude 0.89 (0.59, 1.36) Adj. 0.86 (0.54, 1.37)
Miscarriage	2005 (6.6)	8778 (7.0)	2869 (12.8)	Crude 0.94 (0.89, 1.00) Adj. **0.93 (0.88, 1.00)**	Crude 0.51 (0.48, 0.55) Adj. **0.67 (0.62, 0.72)**
Ectopic	339 (1.1)	1064 (0.9)	181 (0.8)	Crude 1.31 (1.12, 1.54) Adj. **1.31 (1.11, 1.56)**	Crude 1.38 (1.09, 1.74) Adj. 1.16 (0.90, 1.50)
Induced abortion	9537 (31.2)	30573 (24.3)	1540 (6.9)	Crude 1.29 (1.25, 1.32) Adj. **1.33 (1.30, 1.37)**	Crude 4.55 (4.25, 4.86) Adj. **4.37 (4.06, 4.70)**
Outcomes in ongoing pregnancies	**Induced Abortion N=18646**	**Live birth N=85440**	**Miscarriage N=17814**	**Crude and Adjusted (Adj.) Relative Risk (99% CI) [2]**	
Pre-eclampsia	144 (0.8)	567 (0.7)	165 (0.9)	Crude 1.16 (0.92, 1.48) Adj. **1.40 (1.10, 1.79)**	Crude 0.83 (0.62, 1.12) Adj. 0.91 (0.66, 1.27)
Placenta previa	183 (1.0)	473 (0.6)	133 (0.8)	Crude 1.77 (1.42, 2.22) Adj. **1.78 (1.40, 2.25)**	Crude 1.32 (0.98, 1.76) Adj. 1.34 (0.97, 1.84)
Abruptio placenta	91 (0.5)	325 (0.4)	66 (0.4)	Crude 1.28 (0.95, 1.74) Adj. 1.28 (0.93, 1.77)	Crude 1.32 (0.87, 2.00) Adj. 1.32 (0.83, 2.10)
Induction of labour[3]	4298 (23.1)	18239 (21.4)	3968 (22.3)	Crude 1.08 (1.04, 1.12) Adj. **1.11 (1.07, 1.16)**	Crude 1.03 (0.98, 1.09) Adj. 1.01 (0.96, 1.07)
Low birth weight <2500[4]	1086 (5.8)	3905 (4.6)	784 (4.4)	Crude 1.28 (1.17, 1.39) Adj. **1.36 (1.21, 1.51)**	Crude 1.32 (1.17, 1.49) Adj. 1.04 (0.90, 1.21)
Outcomes in spontaneous births	**Induced abortion N=12868**	**Live birth N=59220**	**Miscarriage N=12056**		
Spontaneous preterm birth <37 weeks	859 (6.7)	3035 (5.1)	644 (5.3)	Crude 1.30 (1.18, 1.43) Adj. **1.27 (1.14, 1.40)**	Crude 1.25 (1.10, 1.42) Adj. 1.14 (0.99, 1.32)
Spontaneous very preterm birth <34 weeks	282 (2.2)	929 (1.6)	189 (1.6)	Crude 1.40 (1.17, 1.66) Adj. **1.36 (1.13, 1.64)**	Crude 1.40 (1.10, 1.78) Adj. **1.33 (1.01, 1.74)**

Values are n (%) unless otherwise specified

[1] Adjusted for age, year of delivery, carstairs at second pregnancy & interpregnancy interval

[2] Adjusted for maternal age, year of pregnancy, Carstairs category at second pregnancy & interpregnancy interval

[3] Further adjusted for pre-eclampsia, placenta previa & abruptio placenta

[4] Low birth weight also adjusted for gestational age

TABLE 5: Reproductive outcomes following medical and surgical abortion

Reproductive outcomes in next (2nd) pregnancy	Surgical termination in first pregnancy N=52560	Medical termination in first pregnancy N=16702	Surgical vs Medical induced abortion Crude and Adjusted (Adj.) Relative Risk (99% CI) [1]
Live birth	28285 (53.8)	9785 (58.6)	Crude 0.92 (0.90, 0.94) Adj. 1.44 (1.41, 1.48)
Still birth	151 (0.3)	57 (0.3)	Crude 0.84 (0.56, 1.26) Adj. 0.98 (0.57, 1.69)
Miscarriage	3723 (7.1)	1200 (7.2)	Crude 0.99 (0.91, 1.07) Adj. **1.45 (1.30, 1.62)**
Ectopic	599 (1.1)	120 (0.7)	Crude 1.59 (1.23, 2.05) Adj. **1.78 (1.29, 2.45)**
Induced Abortion	19802 (37.7)	5540 (33.2)	Crude 1.14 (1.10, 1.17) Adj. **0.44 (0.42, 0.46)**
Outcome in ongoing pregnancy	N=28, 436	N=9842	
Pre-Eclampsia	688 (2.4)	316 (3.2)	Crude 0.75 (0.63, 0.90) Adj. 1.12 (0.90, 1.39)
Placenta praevia	248 (0.9)	23 (0.2)	Crude 3.73 (2.13, 6.54) Adj. **2.23 (1.17, 4.26)**
Abruptio placentae	160 (0.6)	40 (0.4)	Crude 1.38 (0.88, 2.18) Adj. 1.09 (0.63, 1.88)
Birth weight [2] <2500 g	2407 (8.5)	697 (7.1)	Crude 1.19 (1.07, 1.33) Adj. 1.12 (0.97, 1.28)
Spontaneous births	**N=18126**[3]	**N=6474**[3]	
Preterm <37 wks	1768 (9.8)	533 (8.2)	Crude 1.18 (1.05, 1.34) Adj. **1.25 (1.07, 1.45)**
Very Preterm <34 wks	633 (3.5)	217 (3.4)	Crude 1.04 (0.86, 1.27) Adj. 1.09 (0.84, 1.40)

Values are n (%) unless otherwise specified

[1] All relative risks have been adjusted for maternal age, year of event, Carstairs category at the previous & interpregnancy interval

[2] Low birth weight also adjusted for gestational age

[3] Only spontaneous delivery considered among live & still birth

TABLE 6: Comparisons of perinatal outcomes following one or more induced abortions

	No of consecutive previous induced abortions				Crude and Adjusted[1] (Adj.) Relative Risks for perinatal outcomes after 2, 3 and 4 abortions compared to 1 abortion (99% confidence Interval)					
	1 N=25348	**2 N=3622**	**3 N=565**	**4 N=225**	**2 vs 1[4]**		**3 vs 1[4]**		**4 vs 1[4]**	
Low birth weight <2500g [2, 3]	2188 (8.6)	325 (9.0)	54 (9.6)	20 (8.9)	Crude Adj.	1.04 (0.90, 1.20) 0.92 (0.77, 1.11)	Crude Adj.	1.11 (0.79, 1.55) 0.99 (0.73, 1.34)	Crude Adj.	1.03 (0.59, 1.79) 0.54 (0.25, 1.16)
Induction of labour	6919 (27.3)	1005 (27.8)	170 (30.1)	72 (32.0)	Crude Adj.	1.02 (0.94, 1.09) 1.02 (0.95, 1.10)	Crude Adj.	1.10 (0.93, 1.30) 1.11 (0.94, 1.31)	Crude Adj.	1.17 (0.91, 1.51) 1.20 (0.93, 1.55)
	N=16275	**N=2285**	**N=347**	**N=136**						
Spontaneous preterm birth <37 weeks	1676 (10.3)	243 (10.6)	37 (10.7)	20 (14.7)	Crude Adj.	1.03 (0.88, 1.22) 0.94 (0.81, 1.10)	Crude Adj.	1.04 (0.69, 1.55) 1.06 (0.76, 1.47)	Crude Adj.	1.43 (0.84, 2.44) 0.92 (0.53, 1.61)
Spontaneous preterm birth <34weeks	613 (3.8)	87 (3.8)	17 (4.9)	9 (6.6)	Crude Adj.	1.01 (0.76, 1.35) 0.96 (0.71, 1.28)	Crude Adj.	1.30 (0.70, 2.41) 1.14 (0.60, 2.14)	Crude Adj.	1.76 (0.76, 4.05) 1.61 (0.69, 3.72)

Values are n (%) unless otherwise specified

[1] All relative risks have been adjusted for maternal age, year of event, Carstairs category & interpregnancy interval.

[2] Low birth weight also adjusted for gestational age

[3] Percentage calculated based on number available in the group

[4] Comparison group is women with 1 IA

Reproductive outcomes following ectopic pregnancy: a national register based cohort study in Scotland

Supplemental file: STROBE Statement

Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Location within manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title & Abstract: Line 51
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract: Lines 52 - 97
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction: Lines 112 - 159
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction: Lines 161-170
Methods			
Study design	4	Present key elements of study design early in the paper	Methodology: Line 173
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods Lines 178-181
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods: Lines 178 - 207
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods: Lines 213 - 221
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods: Lines 210 - 211.
Bias	9	Describe any efforts to address potential sources of bias	The only possible source of bias could be misclassification of variables as routinely collected data are used. We think that the large dataset should

			compensate for that.
Study size	10	Explain how the study size was arrived at	All available data were included. Power calculation: lines 225 -235.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis: Lines 238-267
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis: Lines 238-267
		(*b*) Describe any methods used to examine subgroups and interactions	Methods: Lines 203 - 207
		(*c*) Explain how missing data were addressed	Methodology: Lines 152 - 159
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable.
		(*e*) Describe any sensitivity analyses	Methodology Lines 261-267
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results: Lines 176 - 177
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	The whole population was selected
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1 and 3
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 and 3
		(c) Summarise follow-up time (eg, average and total amount)	Table 1 and 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2,4,5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 4, 5
		(*b*) Report category boundaries when	Methods, Tables 2, 4, 5

		continuous variables were categorized	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results: Lines 266-7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion: Lines 341-353
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion: Lines 377-389
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion: Lines 439-449
Generalis-ability	21	Discuss the generalisability (external validity) of the study results	Discussion: Lines 363-373

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Lines 479-480

Reproductive outcomes following induced abortion: a national register based cohort study in Scotland

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000911.R1
Article Type:	Research
Date Submitted by the Author:	24-May-2012
Complete List of Authors:	Bhattacharya, Siladitya; University of Aberdeen, Institute of Applied Health Sciences Lowit, Alison; University of Aberdeen, Institute of Applied Health Sciences Bhattacharya, Sohinee; University of Aberdeen, Public Health Raja, Edwin Amalraj; University of Aberdeen, Medical Statistics, Dept. of Public Health Lee, Amanda; University of Aberdeen, Medical Statistics, Dept. of Public Health Mahmood, Tahir; Forth Park Hospital, Obstetrics and Gynaecology Templeton, Allan; University of Aberdeen, Institute of Applied Health Sciences
Primary Subject Heading:	Reproductive medicine, obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS, PERINATOLOGY, REPRODUCTIVE MEDICINE

Reproductive outcomes following induced abortion: a national register based cohort study in Scotland

Siladitya Bhattacharya[1], Alison Lowit[1] Sohinee Bhattacharya[1*], Edwin A Raja[1], Amanda J Lee[1], Tahir Mahmood[2], Allan Templeton[1]

[1]Division of Applied Health Sciences, University of Aberdeen
[2]Forth Park Hospital, Kirkcaldy

*Corresponding author

All correspondence to:
Sohinee Bhattacharya
Lecturer, Obstetric Epidemiology
University of Aberdeen
Dugald Baird Centre for Research on Women's Health
Aberdeen Maternity Hospital
AB25 2ZL
Tel: +44 (0)1224 438441
e-mail: sohinee.bhattacharya@abdn.ac.uk

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: The Chief Scientist Office Scotland funded the study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Abstract

Background

The impact of induced abortions on subsequent childbearing is of major importance to women. Some published studies have shown a link between induced abortion and subsequent preterm birth but existing studies have been largely unable to disentangle spontaneous and induced preterm delivery. The primary aim of this study was to investigate reproductive outcomes in women following induced abortion.

Methods

Data were extracted on all women (aged 15-55 years) who had an induced abortion, a miscarriage, a livebirth, or an ongoing pregnancy and live delivery in their first pregnancy recorded between 1981 and 2007 in the Scottish Morbidity Records databases. Obstetric and perinatal outcomes in a second ongoing pregnancy following an induced abortion were compared with those in primigravidae, as well as those who had had a miscarriage or livebirth in their first pregnancy. Spontaneous preterm birth rates were also compared in women following surgical and medical termination as well as after one or more consecutive induced abortions.

Findings

A total of 120,033, 457,477 and 47,355 women with a documented second pregnancy following an initial induced abortion (IA), livebirth and miscarriage respectively between 1981 and 2007 were identified. Data from first pregnancies from the 457,477 women who had an initial livebirth constituted a third unexposed cohort of primigravidae. Women who underwent an initial induced abortion were younger and more socially deprived than those who had a livebirth or a miscarriage ($p<0.001$). The livebirth group contained the highest proportion of current smokers, followed by the abortion group.

Women with an induced abortion in a first pregnancy had a higher risk of spontaneous preterm live birth in the next pregnancy than women in their first pregnancies [Adjusted relative risk (Adj. RR) 1.37, 99% Confidence Interval (CI) 1.32, 1.43] or women who had a livebirth in their first pregnancy [Adj. RR 1.66, 99% CI 1.58-1.74], but a lower risk in comparison with women with a previous miscarriage [Adj. RR 0.85, 99% CI 0.79-0.92]

Following an initial induced abortion, women were more likely to be diagnosed with placental abruption than either primigravidae [Adj. RR 1.28, 99% CI 1.10-

1.50] or women with a previous livebirth [Adj. RR 1.49, 99% CI 1.25-1.77]. The risk of pre-eclampia was higher in women with previous induced abortion in comparison with primigravidae [Adj. RR 1.26, 99% CI 1.17-1.35] or women with a previous livebirth [Adj. RR 2.42, 99% CI 2.21- 2.65].

In comparison with women who had an initial miscarriage, women with an IA in their first pregnancy were less likely to have a subsequent miscarriage [Adj. RR 0.56, 99% CI 0.54-0.590] or ectopic pregnancy [Adj. RR 0.83, 95% CI 0.71-0.97] but more likely to have a second induced abortion [Adj. RR 4.64, 99% CI 4.44-4.85]. They were less prone to develop pre-eclampsia [Adj. RR 0.83, 99% CI 0.73-0.94] in their next ongoing pregnancy.

Surgical abortion was associated with a higher chance of spontaneous preterm birth in the next ongoing pregnancy than medical abortion [Adj. RR 1.25, 99% CI 1.07-1.45)]. Compared with primigravid women, the risk of spontaneous preterm delivery was higher after surgical (Adj. RR 1.45 (1.37, 1.55) but not medical abortion (1.11 (0.99, 1.24). The adjusted relative risks (99% CI) for spontaneous preterm birth in the next ongoing pregnancy following two, three and four consecutive IAs in comparison with a single IA were 1.02 (0.86-1.21), 1.01 (0.66-1.55) and 1.38 (0.71-2.70) respectively.

Interpretation

Induced abortion in a first pregnancy is associated with a higher risk of spontaneous pretermbirth in a subsequent pregnancy than that in primigravidae or women with a previous livebirth, but is lower than that observed in women with an initial miscarriage. This is the first study to show that surgical, but not medical abortion appears to be associated with an increased risk of spontaneous preterm birth.

Background

Many women start their reproductive careers with an abortion in their first pregnancy. In 2009, 13,005 abortions were performed in Scotland with the highest rates in women aged 16-19 years [1]. What is not yet entirely clear is the effect these abortions may have on subsequent childbearing. It has been believed that infection, cervical trauma and endometrial curettage associated with induced abortion could lead to future infertility, ectopic, preterm delivery and placenta praevia, but the data from existing observational studies are mixed [2-18] Following the legalisation of abortion in 1967, initial research on the effects of an induced abortion on subsequent pregnancies showed no evidence of an increased risk of miscarriage, preterm delivery or low birth weight[19, 20]. Much of the work in the subject has been hampered by methodological limitations; randomised controlled studies are not feasible in this context and researchers have looked to observational studies. Many of the published studies have been limited by small sample sizes, self-reported outcomes and inability to adjust for many potential confounders. A recent review [21] reported that half of the twelve relevant studies found an association between induced abortion and preterm birth as well placenta praevia. More recently a number of large studies found no increased risk of placenta praevia, but supported an association with preterm [18, 22, 23] and very preterm delivery [24, 25] The clinical implications of this are profound as reducing the incidence of preterm delivery, with its considerable associated problems, remains one of the most significant challenges in obstetrics.

Over a quarter of induced abortions in Scotland in 2005 were repeat procedures [1] [ISD, personal communication]. While the reproductive sequalae of repeat abortions are unclear, the available literature suggests that the risk of preterm delivery is increased by multiple abortions [18, 22, 24, 26].

Changes in the technique of abortion have to be taken into account when assessing their impact on future reproduction. In 1992, 83.6% of terminations were carried out surgically, falling to 60.6% in 1998 and 40.7% in 2006, with the reminder being carried out medically [1]accessed 23 March 2010. A number of studies [27-29] have compared these methods in terms of safety, efficacy and short term complications but data on subsequent reproductive outcomes is scant. A recent study [30] found no difference in reproductive outcomes (ectopic, miscarriage and preterm delivery) following medically and surgically induced abortions, but was unable to adjust for known confounders such as smoking.

In view of the high current rates of induced abortion, it is important for women and those involved in their care to be aware of any potential associations with future reproductive outcomes.

The Scottish Morbidity Record (SMR) system in Scotland covers a national population and has captured data on medical and surgical abortion for many years. Over 99.3% of abortions in Scotland are carried out in NHS premises and are recorded in the SMR system. As these data are based on clinical records, any potential bias created by underreporting will be removed. The availability of this large national dataset provides an ideal opportunity to link records on abortion (SMR01) with maternity records (SMR02) in order to explore the risk of preterm delivery and other maternal and perinatal outcomes in women following one of more episodes of induced abortion. The data would also allow a meaningful comparison of outcomes following alternative forms of induced abortion (i.e. medical versus surgical).

The primary aim of this study was to investigate reproductive outcomes in women following induced abortion. In particular we wished to answer the following research questions: 1) Is an induced abortion *in a first pregnancy* associated with spontaneous preterm birth or other adverse obstetric or perinatal outcomes in the second pregnancy? 2) Is an induced abortion performed *after a singleton term first pregnancy* associated with spontaneous preterm birth or adverse obstetric or perinatal outcomes in the next pregnancy? 3) Do any of these associations differ by method of induced abortion (i.e. surgical versus medical)? 4) Is the risk of adverse obstetric or perinatal outcomes associated with increasing number of terminations?

Methods

A retrospective cohort study design was used on routinely collected data extracted from the Information and Statistics Division (ISD) database. Approval was obtained from the Privacy Advisory Committee of the National Health Service, Scotland.

Data were extracted from the ISD databases (SMR01 and 02) on women aged 15-55 years who had an induced abortion, a miscarriage, a live birth, or an ongoing pregnancy and live delivery in their first pregnancy between 1981 and 2007 followed by a second pregnancy event. Reproductive outcomes in the subsequent pregnancy of women who had an IA in their first pregnancy (exposed

cohort) were compared with those in two unexposed groups: 1) women in their second pregnancy after a miscarriage in their first pregnancy and 2) women in their second pregnancy after a live birth in their first pregnancy. In addition to these two unexposed cohorts, obstetric and perinatal outcomes in the subsequent pregnancy of women who had an IA in their first pregnancy (exposed group), were also compared with those women in their first pregnancy.

To explore outcomes following early pregnancy loss after an initial livebirth, data were extracted on all women (15-55 years of age) who had an induced abortion, a miscarriage, or a live birth, in their second pregnancy (following a live birth in their first pregnancy) between 1981 and 2007 from the ISD databases (SMR01 and 02) and followed up to identify a third pregnancy event. Reproductive, obstetric and perinatal outcomes in women who had an IA after a singleton term first pregnancy (exposed group), were compared with those in two unexposed groups: 1) women in their third pregnancy following a singleton term delivery in the first pregnancy and a miscarriage in the second pregnancy and 2) women in their third pregnancy following two singleton term deliveries

Women treated by different methods of induced abortion (surgical or medical) in a first pregnancy were compared in terms of reproductive, obstetric and perinatal outcomes. Finally, to answer research question 4, reproductive and perinatal outcomes were compared between women who had 1, 2, 3 and 4 previous consecutive induced abortions and women with no previous abortions. Each group of women was independent of the others – for example women who had 3 abortions were excluded from the group with 2 abortions. For each analysis, except research question 4, the women were matched on parity as the risk of adverse obstetric outcomes is dependent on parity with primiparous women suffering the highest risk.

Data extracted

The following variables were identified by matching SMR01 and SMR02 datasets between the years 1981 and 2007.

Demographic details: Age at pregnancy events, smoking status, and social class (assessed using Carstairs category of deprivation) in the exposed group were compared with each of the 3 unexposed cohorts

Induced abortion details: estimated gestation and method of termination (medical or surgical or both) were recorded for the exposed group. Reproductive outcomes: miscarriage, abortion, livebirth, ectopic, stillbirth in the exposed group were compared with the unexposed cohorts. Obstetric and perinatal outcomes: The incidence of pre-eclampsia, placenta praevia, placental abruption, preterm delivery, very preterm delivery, low birth weight and the mode of delivery in the exposed cohort were compared with each of the 3 unexposed cohorts. Spontaneous delivery rates (including live and stillbirth) were calculated after excluding women who had induced labour and elective (planned) caesarean section.

Socioeconomic status was assessed using the Carstairs index [31] which was divided into quintiles for analysis.

Power Calculation

Given the number of sub-groups in the analysis coupled with multiple outcomes, a global sample size calculation was not feasible. Preliminary enquiries with ISD suggested that we could identify at least 260,000 terminations (1981-2007), of which 30% (n=69,000) were estimated to have had a subsequent live birth and 25.5% (n=66,223) were induced abortions in a first pregnancy.

Using a 1:1 ratio of women with induced abortions in a first pregnancy (exposed cohort) and unexposed women, we anticipated having over 90% power, at the two-sided 5% significance level, to detect a difference of 0.5% or more in the chances of a preterm birth (ie, an odds ratio of 1.09) assuming that the prevalence of live births in the unexposed group was 6%.

Statistical Analysis

In the absence of an ideal comparison group for women with a prior abortion, we used 3 unexposed cohorts which could increase the chance of false positive associations (type I error). To help minimise this, we used a stringent p-value of ≤0.01 to denote statistical significance throughout the statistical analyses.

A generalised linear model was used with Poisson family and robust variance estimator to ascertain the relationship between exposure (first pregnancy induced abortion) and various reproductive outcomes (still birth, miscarriage, ectopic and induced abortion), maternal and perinatal outcomes (pre-eclampsia, placenta-previa, abruption placenta) after adjusting for potential confounders (maternal

age, year of delivery, smoking & carstairs at relevant pregnancy). For the outcome of induction of labour, pre-eclampsia, placenta previa and placental abruption were also entered into the model. Similarly, the outcome low birth weight was also adjusted for gestational age. Stata version 11 was used for the analysis and a stringent p-value of ≤0.01 was used to denote statistical significance throughout.

As smoking data were not routinely collected in the maternity database (SMR02) before 1992, and rarely recorded for women having an induced abortion or miscarriage. Thus self-reported smoking status, collected at antenatal booking visit, though available for some women was non-randomly missing for a high percentage of women. This sometimes led to non-convergence of the statistical models. Therefore, a sensitivity analysis was carried out by re-running all of the multivariate models excluding the smoking variable to determine if the overall effect sizes remained of similar magnitude. This was found to be so.

Results

Demographic characteristics of women who had an abortion in their first pregnancy were compared with those who had either a live birth or a miscarriage in their first pregnancy and with primigravida women (Table 1). Women with a previous induced abortion were significantly older, more socially deprived and more likely to be smokers than primigravida women or those who had a live birth or a miscarriage in a previous pregnancy.

Table 2 presents reproductive outcomes in a subsequent pregnancy following IA, livebirth and miscarriage in the first pregnancy. As Table 2 shows, an IA in the first pregnancy increased the risks of having a still birth or an induced abortion in the second pregnancy as compared with an initial livebirth. Compared to those who had an initial miscarriage, women who had an IA in their first pregnancy were less likely to have a subsequent miscarriage or ectopic pregnancy, but more likely to have another induced abortion.

Perinatal outcomes in the next ongoing pregnancy following IA are also compared with those in primigravida and women who have had a livebirth or miscarriage in Table 2. Compared with women having a previous livebirth, an IA put women at higher risk of pre-eclampsia, abruptio placenta, induction of labour, spontaneous preterm and very preterm delivery (<32weeks) extremely preterm (< 28 weeks) and delivery of a low birth weight baby (<2500 g) but not placenta praevia.

In comparison with women with a previous miscarriage, a history of IA decreased women's chances of developing pre-eclampsia and spontaneous preterm and very preterm delivery. Risks of pre-eclampsia, placental abruption (but not placenta praevia), delivery of a low birth weight baby and spontaneous preterm, very preterm and extremely preterm birth were significantly higher following IA than in primigravid women. The risk of pre-eclampsia in women with a previous IA was higher than in primigravid women but lower than in women with a previous miscarriage (Table 2).

The demographic characteristics of women who had a livebirth in a first pregnancy and then went on to have induced abortion, live birth or a miscarriage in their second pregnancy are shown in Table 3. Women with an induced abortion in their second pregnancy were younger, belonged to a more deprived social group and were more likely to be smokers than women who had a live birth in their second pregnancy. Compared to women who had a miscarriage in their second pregnancy, women with a previous induced abortion were older, belonged to more deprived social classes and were more likely to smoke.

As Table 4 shows, IA in the second pregnancy increased the risks of having ectopic or an induced abortion in the third pregnancy as compared with an initial livebirth. The risk of miscarriage in a third pregnancy was reduced in women who had either an IA in a second pregnancy, but the risks of another induced abortion were higher than in women with a previous miscarriage.

Compared to women with two previous livebirths, women with a livebirth followed by an IA were more likely to have pre-eclampsia, placenta praevia, induced labour, low birthweight and spontaneous preterm, very preterm and extremely preterm birth (Table 4). Women with an IA in a second pregnancy were not at any significantly higher risk of perinatal complications in comparison with women with a previous miscarriage.

In records where the method of IA was clearly recorded, 52,560 women were noted to have had surgical and 16,702, medical abortions. As Table 5 shows, reproductive outcomes were comparable in the two groups except for a lower risk of a second induced abortion following surgical termination of pregnancy. The adjusted relative risk of miscarriage, ectopic pregnancy, placenta praevia and spontaneous preterm delivery (<37 weeks) were significantly higher after surgical termination. In comparison with primigravid women i.e. no previous abortion,

women with a medical abortion had an increased risk of placental abruption, but not spontaneous preterm, very preterm or extremely preterm delivery. In contrast, women with a surgical abortion had higher risks of all three types of spontaneous preterm delivery. They also had an increased risk of preeclampsia, placenta praevia, abruption and low birthweight babies. More women had repeat abortion following surgical termination of pregnancy, and fewer went on to have a livebirth in comparison with primigravid women and those who had medical terminations.

Table 6 summarises the risk of spontaneous preterm delivery in subsequent pregnancies following one or more consecutive IAs in comparison to those with no previous abortions (primigravid women). The adjusted relative risks of spontaneous preterm birth, (< 37 weeks) was incrementally increased in women undergoing 1, 2, 3 and 4 induced abortions. The adjusted relative risk of spontaneous very preterm delivery (< 32 weeks) was increased after 1 and 4 induced abortions. While the adjusted relative risk of spontaneous extremely preterm delivery (<28weeks) was increased by 2 and 4 previous induced abortions. Additional induced abortions did not increase the adjusted relative risks of any type of spontaneous preterm birth after termination of pregnancy.

Discussion

Principal findings

Our results suggest that an induced abortion in the first pregnancy predisposes women to higher maternal and perinatal risks in comparison to women with a previous live birth. Compared to an initial miscarriage, an induced abortion in a first pregnancy led to a higher subsequent risk of miscarriage or ectopic pregnancy, induced abortion and pre-eclampsia. Women with a previous induced abortion face increased risks of antepartum haemorrhage and spontaneous preterm birth than women in their first pregnancy.

A livebirth prior to an IA does not appear to ameliorate perinatal risks in women who are at higher risk of spontaneous preterm birth than primigravida. Surgical termination appears to be associated with a higher chance of spontaneous preterm birth than medical IA. There does not appear to be a dose dependent effect of IA on future adverse perinatal outcomes. Women with three or four consecutive induced abortions were not at significantly higher risk of spontaneous

preterm birth in comparison with women who have had one termination of pregnancy.

Strengths

To our knowledge this is the largest population based study of reproductive outcomes following an induced abortion. Registry based previous studies reporting preterm birth rates as an outcome have been unable to discriminate between spontaneous and induced preterm delivery; this is one of the first papers to be able to calculate and report spontaneous preterm birth rates after induced abortion.

We have acknowledged changes in clinical practice over the years during which data were collected and have adjusted for year of pregnancy in the regression models. The choice of an appropriate comparison group to women with a history of induced abortion is problematic. Women who are pregnant again after having undergone an induced abortion in a previous (first) pregnancy are gravida 2 and parity 0. It is impossible to control for both gravidity and parity unless the unexposed cohort have had a prior pregnancy which did not lead to a delivery. Other comparison groups can be either women in their first ongoing pregnancies (gravidity 1 parity 0), or in their second ongoing pregnancies after a previous delivery (gravidity 2 parity 1). We feel that our strategy comparing the exposed cohort to all three of the above groups adds validity to our results.

Limitations

The main limitations of this study stem from unrecorded and missing data in relation to certain potential confounding factors within the dataset. For example, smoking data were only available for 50% of women; data on body mass index were unavailable while data on gestational age at termination was missing in the majority of cases. The actual method of termination (medical versus surgical) was unrecorded in around 25% of all cases, while a large number of women appeared to have both medical as well as surgical treatment. Parity number was less reliable in the early years of data collection. This may reflect problems with coding and could potentially affect the quality of our results. In addition, the analysis of such a large population based dataset has the capacity to produce statistically significant differences which may or may not be clinically relevant,

although this has been minimised by our use of a stringent 1% significance level throughout.

Defining an ideal reference group is a challenge in studies exploring outcomes after induced abortion. While we have partially addressed this issue by using more than one unexposed cohort, our data do not allow us to adjust for potential differences in pregnancy intentions between groups, which can impact on antenatal care and perinatal outcomes.

Unrecorded data relating to key potential confounders cannot exclude the possibility that some associations are not explained by abortion itself but by special circumstances of women seeking abortion which also increases their risk of complications in pregnancy. We ran a separate analysis to identify previous pregnancy complications in women who either had an induced abortion, miscarriage or livebirth in a second pregnancy. As supplementary Table A shows, induced abortion in the second pregnancy was not significantly associated with increased relative risk (99% confidence interval) of preeclampsia, placenta praevia, placental abruption and low birthweight respectively compared to either livebirth [0.99 (0.85, 1.16); 1.29 (0.99, 1.67) 1.32 (0.96, 1.82) 1.08 (0.98, 1.18)] or miscarriage [0.79 (0.65, 0.96) 1.17 (0.81, 1.69) 1.08 (0.70, 1.68) 1.14 (1.00, 1.30)].

Comparison with previous studies

The association between induced abortion and preterm birth found in this study is consistent with previously published work [32]. Two recent meta-analyses suggest that women who have had an IA are at higher risk of preterm birth in subsequent pregnancies [33, 34]. Our study shows that after adjustment women with a previous abortion have an increased chance of a subsequent preterm birth and very preterm birth compared with primigravidae or those who have had a previous live birth, but at no significantly greater risk compared to women who have had a previous miscarriage. Women who had a live birth before an induced abortion are more likely to have a preterm birth compared to women with two previous live births.

Our results did not suggest a signficant increased risk of miscarriage after an induced abortion which is in keeping with a review of literature [21]. In contrast, Sun (2003)[35] demonstrated an association between surgical abortion and miscarriage in a subsequent pregnancy. Literature on the association between IA and miscarriage or ectopic pregnancy is sparse and conflicting. The increased risk of having a second termination following

induced abortion in a first pregnancy highlighted in our study has been reported elsewhere [36-38]. While women who had an abortion were more likely to have a subsequent abortion, but they may also be more likely to have an unintended pregnancy. This should be seen a potential risk factor which should be explored in future studies.

Available literature suggests there is an association between IA and placenta previa [39, 40], but no association with abruptio placenta [41, 42]. This study found that women in their second pregnancy after an initial induced abortion in the first were at higher odds of both placenta previa and abruptio placenta, women in their third pregnancy after an induced abortion in their second pregnancy had higher odds of placenta previa, but not abruptio placenta. Published evidence supports a decreased risk of pre-eclampsia after an IA [43, 44]. Our results suggest a risk of developing preeclampsia which is on par with primigravid women, but lower than women with a previous miscarriage. The reasons for these associations are unclear and hence any explanations can only be speculative. Problems with placental position and function could occur due to disruption of the endometrium by vigorous curettage. The quality of placental function in a previous pregnancy could influence susceptibility to future preeclampsia.

Since the introduction of medical abortion there has been much speculation about the rival merits of medical and surgical techniques, especially in terms of future reproductive outcomes. Analysis of Danish data has failed to demonstrate a difference in key outcomes such as preterm birth between medical and surgical abortion, but this study was unable to identify spontaneous versus induced preterm birth [30]. With our ability to identify spontaneous PTBs, we have shown a clear association with surgical abortion. However, since we were unable to adjust for gestational age, we cannot rule out the possibility that surgical abortions may have been performed at a more advanced stage of pregnancy requiring a greater degree of cervical dilatation – thus leading to future preterm labour. Our results are supported by a recent publication showing that the risk of preterm birth after one or more medical abortions is higher than after surgical abortion and comparable to that in primigravid women [11].

A dose dependent relationship between the number of IAs and future PTB has been shown in a number of previous studies [32]. The results of our analysis do not

support this. Given our inability to adjust for a number of potential confounders, this needs to be investigated further.

Our data suggest that medical and surgical terminations may impact differently on future reproductive outcomes - with a higher risk of spontaneous preterm birth after surgery. We were unable to disentangle the separate effects of repeated medical and surgical abortion due to a relative paucity of numbers.

A recent publication [11] found an increased risk of premature delivery following multiple surgical, but not first trimester, medical induced abortions. While this could reflect the effect of repeated surgical trauma to the cervix, this needs further exploration in future studies with long term periods of follow up.

A key challenge in studying health sequalae after induced abortion is to deal with potential differences in pregnancy intentions between comparison groups. While women who had an abortion were more likely to have a subsequent abortion, they may also be more likely to have an unintended pregnancy, which needs to be acknowledged as a potential risk factor in future studies.

Conclusions

Induced abortion in a first pregnancy is associated with a higher risk of spontaneous preterm birth in a subsequent pregnancy in comparison with primigravid women, but not women with a previous miscarriage. A successful pregnancy leading to a livebirth prior to an induced abortion does not appear to ameliorate this risk while more than one abortion does not significantly increase it. Surgical abortion appears to be associated with an increased risk of spontaneous very preterm birth in comparison with medical termination of pregnancy. The results of this study should help provide women as well as health professionals with accurate information to inform clinical decision making and tailor antenatal care to address women's risk profiles.

AT conceived the idea for the study. SB was the Principal Investigator. He designed the study along with SohB, AT, ALee and TM, led the funding application, managed the project, interpreted the results and wrote the first draft of the paper. ALo cleaned the data and performed some of the initial analyses. SohB co-wrote the funding application, facilitated data manipulation, interpreted the results and helped to draft the paper. EAR performed the statistical analysis and interpreted the results with input from ALee. All authors commented on, and contributed to the final draft of the paper.

Acknowledgements

We thank staff at ISD Scotland for extraction of data from the Scottish Morbidity Records Database and Margery Heath for secretarial assistance.

Funding

The Chief Scientist Office Scotland funded the study. The views expressed are those of the authors and not the funding body.

References

1. Available at: http://www.isdscotland.org/isd/CCC_FirstPage.jsp-.

2. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiol Rev* 1993;15(2):414-43.

3. Calhoun BC, Shadigian E, Rooney B. Cost consequences of induced abortion as an attributable risk for preterm birth and impact on informed consent. *J Reprod Med* 2007; Oct;52(10):929-37.

4. Chen A, Yuan W, Meirik O, Wang X, Wu SZ, Zhou L, et al. Mifepristone-induced early abortion and outcome of subsequent wanted pregnancy. *Am J Epidemiol* 2004; Jul 15;160(2):110-7.

5. de Haas I, Harlow BL, Cramer DW, Frigoletto FD,Jr. Spontaneous preterm birth: a case-control study. *Am J Obstet Gynecol* 1991; Nov;165(5 Pt 1):1290-6.

6. Foix-L'Helias L, Blondel B. Changes in risk factors of preterm delivery in France between 1981 and 1995. *Paediatr Perinat Epidemiol* 2000; Oct;14(4):314-23.

7. Freak-Poli R, Chan A, Tucker G, et al. Previous abortion and risk of pre-term birth: a population study. *J Maternal-Fetal & Neonatal Med* 2009;22(1):1-7.

8. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; Jan 5;371(9606):75-84.

9. Lang JM, Lieberman E, Cohen A. A comparison of risk factors for preterm labor and term small-for-gestational-age birth. *Epidemiology* 1996; Jul;7(4):369-76.

10. Lekea-Karanika V, Tzoumaka-Bakoula C, Golding J. Previous obstetric history and subsequent preterm delivery in Greece. *Eur J Obstet Gynecol Reprod Biol* 1990; Nov;37(2):99-109.

11. Liao H, Wei Q, Duan L, Ge J, Zhou Y, Zeng W. Repeated medical abortions and the risk of preterm birth in the subsequent pregnancy. *Arch Gynecol Obstet* 2011; Sep;284(3):579-86.

12. Martius JA, Steck T, Oehler MK, Wulf KH. Risk factors associated with preterm (<37+0 weeks) and early preterm birth (<32+0 weeks): univariate and multivariate analysis of 106,345 singleton births from the 1994 statewide perinatal survey of Bavaria. *European Journal of Obstetrics Gynecology and Reproductive Biology* 1998;80(2):183,184-189.

13. Pickering RM, Deeks JJ. Risks of delivery during the 20th to the 36th week of gestation. *Int J Epidemiol* 1991; Jun;20(2):456-66.

14. Reime B, Schucking BA, Wenzlaff P. Reproductive outcomes in adolescents who had a previous birth or an induced abortion compared to adolescents' first pregnancies. *BMC Pregnancy Childbirth* 2008; Jan 31;8:4.

15. Voigt M, Olbertz D, Fusch C, Krafczyk D, Briese V, Schneider KT. The influence of previous pregnancy terminations, miscarriages and still-births on the incidence of babies with low birth weight and premature births as well as a somatic classification of newborns. *Z Geburtshilfe Neonatol* 2008; Feb;212(1):5-12.

16. Watson LF, Rayner JA, King J, Jolley D, Forster D, Lumley J. Modelling sequence of prior pregnancies on subsequent risk of very preterm birth. *Paediatr Perinat Epidemiol* 2010; Sep;24(5):416-23.

17. Winer N, Resche-Rigon M, Morin C, Ville Y, Rozenberg P. Is induced abortion with misoprostol a risk factor for late abortion or preterm delivery in subsequent pregnancies?. *Eur J Obstet Gynecol Reprod Biol* 2009; Jul;145(1):53-6.

18. Zhou W, Sorensen HT, Olsen J. Induced abortion and subsequent pregnancy duration. *Obstet Gynecol* 1999; Dec;94(6):948-53.

19. Atrash HK, Hogue CJ. The effect of pregnancy termination on future reproduction. *Baillieres Clin Obstet Gynaecol* 1990; Jun;4(2):391-405.

20. Hogue CJ. Impact of abortion on subsequent fecundity. *Clinics in Obstetrics & Gynaecology* 1986;13(1):95,96-103.

21. Thorp JM, Hartmann KE, Shadigian E. Long-term physical and psychological health consequences of induced abortion: review of the evidence. *Obstet Gynecol* Survey 2002; 58;1(67):79.

22. Ancel PY, Lelong N, Papiernik E, et al. History of induced abortion as a risk factor for preterm birth in European countries: results from the EUROPOP survey. *Hum Reprod* 2004;19(3):734-40.

23. Raatikainen K, Heiskanen N, Heinonen S. Induced abortion: not an independent risk factor for pregnancy outcome, but a challenge for health counseling. *Ann Epidemiol* 2006; Aug;16(8):587-92.

24. Moreau C, Kaminski M, Ancel PY, Bouyer J, Escande B, Thiriez G, et al. Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study. *BJOG* 2005; Apr;112(4):430-7.

25. Zhou W, Nielsen GL, Larsen H, Olsen J. Induced abortion and placenta complications in the subsequent pregnancy. *Acta Obstet Gynecol Scand* 2001; Dec;80(12):1115-20.

26. Henriet L, Kaminski M. Impact of induced abortions on subsequent pregnancy outcome: the 1995 French national perinatal survey. *BJOG* 2001; Oct;108(10):1036-42.

27. Henshaw RC, Naji SA, Russsell IT, Templeton A. A comparison of medical abortion (using mifepristone and gemeprost) with surgical vacuum aspiration: efficacy and early medical sequelae. *Human Reproduction* 1994;9(11):2167,2168-2171.

28. Ashok PW, Kidd A, Flett GM, Fitzmaurice A, Graham W, Templeton A. A randomized colmparison of medical abortin and surgical vacuum aspiration at 10-13 weeks gestation. *Human Reproduction* 2002;17(1):92,93-98.

29. Rorbye C, Norgaard M, Nilas L. Medical versus surgical abortion efficacy, complications and leave of absence compared in a partly randomized study. *Contraception 2004* 2004;70(5):393,394-399.

30. Virk J, Zhang J, Olsen J. Medical abortion and the risk of subsequent adverse pregnancy outcomes. *N Engl J Med* 2007; Aug 16;357(7):648-53.

31. Carstairs V MR. Deprivation and Health in Scotland 1991;.

32. Lowit A, Bhattacharya S. Obstetric performance following an induced abortion. *Best Practice & Research - Clinical Obstetrics & Gynaecology* 2010;24(5):667,668-82.

33. Shah PS, Zao J. Induced termination of pregnancy and low birth weight and preterm birth: a systemic review and meta-analysis. *BJOG* 2009;116:1425-42.

34. Swingle HM, Colaizy TT, Zimmerman MB, et al. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analysis. *J Reprod Med* 2009;54:95-108.

35. Sun Y, Che Y, Ershang G, et al. Induced abortion and risk of subsequent miscarriage. *Int J Epidemiol* 2003; 32;(449):454.

36. Heikinheimo O, Gissler M, Suhonen S. Age, parity, history of abortion and contraceptive choices affect the risk of repeat abortions. *Contraception 2008* 2008;:149,150-154.

37. Prager SW, Steinauer JE, Foster DF, Darney PD, Drey EA. Risk factors for repeat elective abortion. *American Journal of Obstetrics & Gynecology* 2007;197:e1-575,576-e6.

38. Rowlands S. More than one abortion. *Joural Fam Plann Reprod Health Care* 2007;33(3):155,156-158.

39. Ananth CV, Smulian JC, Vintzileos AM. The effect of placenta previa on neonatal mortality: a population-based study in the United States, 1989 through 1997. *Am J Obstet Gynecol* 2003; May;188(5):1299-304.

40. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta abruption in an Asian population. *Reproductive Sciences* 2007;14(1):59-65.

41. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta previa in an Asian population. *Int J Gynecol & Obstet* 2007;97:26-30.

42. Zhu QX, Gao ES, Chen AM, et al. Mifepristone-induced abortion and placenta complications in subsequent pregnancy. *Hum Reprod* 2009;24(2):315-9.

43. Eras JL, Saftlas AF, Triche E, et al. Abortion and its effect on risk of pre-eclampsia and transient hypertension. *Epidemiology* 2000;11:36-43.

44. Trogstad L, Magnus P, Skjaerven R, et al. Previous abortions and risk of pre-eclampsia. *Int J Epidemiology* 2008;37:1333-40.

647

TABLE 1: Demographic characteristics at first pregnancy of women who had induced abortion, livebirth or miscarriage in their first pregnancy

		Outcome in first pregnancy				
		Induced abortion N=120,033	**Live birth N=457,477**	**p-value**	**Miscarriage N=47,355**	**p-value**
Mean Age (SD)		24.68 (7.56)	24.89 (5.11)	<0.001	26.26 (6.13)	<0.001
Carstairs Category [1,2]	1	17265 (17.1)	79705 (18.0)	<0.001	8403 (18.8)	<0.001
	2	18538 (18.3)	81661 (18.4)		8206 (18.4)	
	3	19530 (19.3)	84559 (19.1)		8794 (19.7)	
	4	21135 (20.9)	92504 (20.9)		9426 (21.1)	
	5	24615 (24.4)	105313 (23.7)		9788 (21.9)	
Smoking status[2]	Never	1014 (42.3)	112744 (48.4)	<0.001	4892 (39.8)	<0.001
	Current	676 (28.2)	72182 (31.0)		2044 (16.6)	
	Former	85 (3.5)	22140 (9.5)		533 (4.3)	
	Not known	622 (26.0)	26088 (11.2)		4818 (39.2)	
	Total	2397	233154		12287	
	Missing	117636 (98.0)	224323 (49.0)		35068 (74.1)	
Interpregnancy interval in Weeks	Median (IQR)	165 (78, 321)	139 (95, 213)	<0.001	65 (47, 104)	<0.001

651 Values are n (%) unless otherwise specified

652 [1] Carstairs categories 1 = least deprived, 5 = most deprived

653 [2] Percentage based on available information for each group

654

655 **TABLE 2: Reproductive and perinatal outcomes following induced abortion, miscarriage or live birth in first pregnancy**

Outcome of 2nd pregnancy	**Outcome in First pregnancy**				**Crude and Adjusted (Adj.) Relative Risk (99% CI)** [1]		
	Induced abortion N=120033	**Live birth N=457477**	**Miscarriage N=47355**		**Induced abortion vs Live birth**	**Induced abortion vs Miscarriage**	
Live birth	67336 (56.1)	355674 (77.7)	36479 (77.0)		Crude **0.72 (0.71, 0.73)** Adj. **0.74 (0.73, 0.74)**	Crude **0.72 (0.72, 0.73)** Adj. **0.69 (0.69, 0.70)**	
Still birth	409 (0.34)	1406 (0.31)	247 (0.52)		Crude 1.11 (0.96, 1.28) Adj. 1.06 (0.91, 1.24)	Crude **0.65 (0.53, 0.80)** Adj. **0.58(0.46, 0.74)**	
Miscarriage	7965 (6.6)	30669 (6.7)	6197 (13.1)		Crude 0.99 (0.96, 1.02) Adj. **1.05(1.01, 1.08)**	Crude **0.51 (0.49, 0.53)** Adj. **0.56(0.54, 0.59)**	
Ectopic	1115 (0.9)	2939 (0.6)	499 (1.1)		Crude **1.45 (1.32, 1.58)** Adj. **1.36(1.23, 1.50)**	Crude 0.88 (0.77, 1.01) Adj. **0.83(0.71, 0.97)**	
Induced abortion	43208 (36.0)	66789 (14.6)	3933 (8.3)		Crude **2.47 (2.43, 2.50**) Adj. **2.30(2.27, 2.33)**	Crude **4.33 (4.16, 4.51)** Adj. **4.64(4.44, 4.85)**	
Outcomes in ongoing pregnancies	**N=67745**	**N=357080**	**N=36726**	**Primigravida N=457477**			**Induced abortion vs Primigravida**
Pre-eclampsia	1583 (2.3)	2982 (0.8)	922 (2.5)	8649 (1.9)	Crude **2.80 (2.58, 3.03)** Adj. **2.42 (2.21, 2.65)**	Crude 0.93 (0.84, 1.03) Adj. **0.83 (0.73, 0.94)**	Crude **1.24 (1.15, 1.32)** Adj. **1.26 (1.17, 1.35)**
Placentaprevia	385 (0.6)	1919 (0.5)	289 (0.8)	2042 (0.5)	Crude 1.06 (0.92, 1.22) Adj. 1.09 (0.93, 1.28)	Crude **0.72 (0.59, 0.88)** Adj. 0.79 (0.62, 1.01)	Crude **1.27 (1.10, 1.47)** Adj. 1.05 (0.91, 1.22)
Abruptio placenta	339 (0.5)	1197 (0.3)	173 (0.5)	1770 (0.4)	Crude **1.49 (1.27, 1.75)** Adj. **1.49 (1.25, 1.77)**	Crude 1.06 (0.84, 1.35) Adj. 1.00 (0.76, 1.32)	Crude **1.30 (1.11, 1.51)** Adj. **1.28 (1.10, 1.50)**
Induction of labour[2]	18044 (26.6)	69482 (19.5)	10347 (28.2)	120080 (26.3)	Crude **1.37 (1.34, 1.39)** Adj. **1.33 (1.30, 1.35)**	Crude **0.95 (0.92, 0.97)** Adj. 0.98 (0.95, 1.01)	Crude 1.01 (1.00, 1.03) Adj. 1.00 (0.99, 1.02)
Low birth weight <2500g[3]	5385 (8.0)	16309 (4.6)	3101 (8.5)	28735 (6.3)	Crude **1.74 (1.67, 1.81)** Adj. **1.24 (1.17, 1.31)**	Crude 0.94 (0.89, 1.00) Adj. 0.96 (0.90, 1.03)	Crude **1.27 (1.22, 1.31)** Adj. **1.08 (1.04, 1.13)**

Outcomes in spontaneous births	N= 45656	N=255220	N=23751	N=318217			
Spontaneous preterm birth <37 weeks	4224 (9.3)	13453 (5.3)	2376 (10.0)	21891 (6.9)	Crude **1.76 (1.68, 1.83)** Adj. **1.66 (1.58, 1.74)**	Crude **0.92 (0.86, 0.99)** Adj. **0.85 (0.79, 0.92)**	Crude **1.35 (1.29, 1.40)** Adj. **1.37 (1.32, 1.43)**
Spontaneous very preterm birth <32 weeks	878 (1.9)	2157 (0.9)	513 (2.2)	4051 (1.3)	Crude **2.28 (2.05, 2.52)** Adj. **2.20 (1.96, 2.47)**	Crude 0.89 (0.77, 1.03) Adj. **0.83 (0.70, 0.99)**	Crude **1.51 (1.37, 1.66)** Adj. **1.57 (1.43, 1.72)**
Spontaneous very preterm birth <28 weeks	271 (0.6)	651 (0.3)	186 (0.8)	1349 (0.4)	Crude **2.33 (1.93, 2.80)** **Adj. 2.24 (1.82, 2.76)**	Crude **0.76 (0.59, 0.97)** Adj. 0.80 (0.60, 1.06)	Crude **1.40 (1.18, 1.66)** **Adj. 1.49 (1.26, 1.77)**

Values are n (%) unless otherwise specified

1 Adjusted for maternal age, year of delivery, Carstairs at first pregnancy & interpregnancy interval.

2 Further adjusted for pre-eclampsia, placenta previa & abruptio placenta.

3 Low birth weight also adjusted for gestational age.

TABLE 3: Demographic characteristics of women who had induced abortion, livebirth or miscarriage after an initial livebirth

		Outcome in second pregnancy following an initial livebirth				
		Induced abortion N=30527	**Live birth N=125855**	**p-value**	**Miscarriage N=22404**	**p-value**
Mean Age (SD)		26.04 (5.85)	26.15 (4.68)	<0.001	28.41 (5.42)	0.001
Carstairs Category[1,2]	1	3523 (12.8)	20264 (16.5)	<0.001	4498 (20.9)	<0.001
	2	4304 (15.6)	21985 (17.9)		4079 (18.9)	
	3	5186 (18.8)	23425 (19.0)		4312 (20.0)	
	4	6243 (22.6)	25979 (21.1)		4447 (20.6)	
	5	8370 (30.3)	31395 (25.5)		4235 (19.6)	

Smoking status[2]	Never	393 (39.7)	32464 (48.5)	<0.001	3165 (46.1)	0.001
	Current	313 (31.6)	20658 (30.9)		1169 (17.0)	
	Former	43 (4.3)	5359 (8.0)		282 (4.1)	
	Not known	241 (24.3)	8482 (12.7)		2243 (32.7)	
	Total	990	66963		6859	
	Missing	29537 (96.8)	58892 (46.8)		15545 (69.4)	
Interpregnancy interval	Median(IQR)	108 (61, 209)	152 (96, 256)	<0.001	60 (48, 87)	<0.001

Values are n (%) unless otherwise specified

[1] Carstairs categories 1 = least deprived, 5 = most deprived

[2] Percentage based on available information for each group

TABLE 4: Reproductive and perinatal outcomes in women who had induced abortion, livebirth or miscarriage following a livebirth in the first pregnancy

Outcome of 3rd pregnancy	**Outcome of second pregnancy**			**Crude and Adjusted (Adj.) Relative Risk (99% CI)** [1]	
	Induced abortion N=30527	**Live birth N=125855**	**Miscarriage N=22404**	**Induced abortion vs Live birth**	**Induced abortion vs Miscarriage**
Live birth	18562 (60.8)	85014 (67.5)	17745 (79.2)	**Crude 0.90 (0.89, 0.91)** **Adj. 0.88 (0.87, 0.89)**	**Crude 0.77 (0.76, 0.78)** **Adj. 0.77 (0.76, 0.78)**
Still birth	84 (0.3)	426 (0.3)	69 (0.3)	Crude 0.81 (0.60, 1.11) Adj. 0.76 (0.55, 1.06)	Crude 0.89 (0.59, 1.36) Adj. 0.86 (0.54, 1.37)
Miscarriage	2005 (6.6)	8778 (7.0)	2869 (12.8)	Crude 0.94 (0.89, 1.00) Adj. 0.93 (0.88, 1.00)	Crude **0.51 (0.48, 0.55)** Adj. **0.67 (0.62, 0.72)**
Ectopic	339 (1.1)	1064 (0.9)	181 (0.8)	**Crude 1.31 (1.12, 1.54)** **Adj. 1.31 (1.11, 1.56)**	**Crude 1.38 (1.09, 1.74)** **Adj. 1.16 (0.90, 1.50)**
Induced abortion	9537 (31.2)	30573 (24.3)	1540 (6.9)	**Crude 1.29 (1.25, 1.32)** **Adj. 1.33 (1.30, 1.37)**	**Crude 4.55 (4.25, 4.86)** **Adj. 4.37 (4.06, 4.70)**
Outcomes in ongoing pregnancies	**Induced Abortion N=18646**	**Live birth N=85440**	**Miscarriage N=17814**	**Crude and Adjusted (Adj.) Relative Risk (99% CI)** [2]	
Pre-eclampsia	144 (0.8)	567 (0.7)	165 (0.9)	Crude 1.16 (0.92, 1.48) Adj. **1.40 (1.10, 1.79)**	Crude 0.83 (0.62, 1.12) Adj. 0.91 (0.66, 1.27)
Placenta previa	183 (1.0)	473 (0.6)	133 (0.8)	**Crude 1.77 (1.42, 2.22)** **Adj. 1.78 (1.40, 2.25)**	Crude 1.32 (0.98, 1.76) Adj. 1.34 (0.97, 1.84)
Abruptio placenta	91 (0.5)	325 (0.4)	66 (0.4)	Crude 1.28 (0.95, 1.74) Adj. 1.28 (0.93, 1.77)	Crude 1.32 (0.87, 2.00) Adj. 1.32 (0.83, 2.10)
Induction of labour[3]	4298 (23.1)	18239 (21.4)	3968 (22.3)	**Crude 1.08 (1.04, 1.12)** **Adj. 1.11 (1.07, 1.16)**	Crude 1.03 (0.98, 1.09) Adj. 1.01 (0.96, 1.07)
Low birth weight <2500[4]	1086 (5.8)	3905 (4.6)	784 (4.4)	**Crude 1.28 (1.17, 1.39)** **Adj. 1.36 (1.21, 1.51)**	Crude **1.32 (1.17, 1.49)** Adj. 1.04 (0.90, 1.21)
Outcomes in spontaneous births	**Induced abortion N=12868**	**Live birth N=59220**	**Miscarriage N=12056**		
Spontaneous preterm birth <37 weeks	859 (6.7)	3035 (5.1)	644 (5.3)	**Crude 1.30 (1.18, 1.43)** **Adj. 1.27 (1.14, 1.40)**	Crude **1.25 (1.10, 1.42)** Adj. 1.14 (0.99, 1.32)
Spontaneous very preterm birth <32 weeks	162 (1.3)	495 (0.8)	104 (0.9)	**Crude 1.51 (1.19, 1.90)** **Adj. 1.44 (1.12, 1.84)**	Crude **1.46 (1.06, 2.01)** Adj. 1.35 (0.93, 1.96)

Spontaneous very preterm birth <28 weeks	55 (0.4)	152 (0.3)	38 (0.3)	**Crude 1.67 (1.11, 2.49)** **Adj. 1.59 (1.02, 2.46)**	Crude 1.36 (0.79, 2.33) Adj. 1.19 (0.62, 2.30)

Values are n (%) unless otherwise specified

[1] Adjusted for age, year of delivery, carstairs at second pregnancy & interpregnancy interval

[2] Adjusted for maternal age, year of pregnancy, Carstairs category at second pregnancy & interpregnancy interval

[3] Further adjusted for pre-eclampsia, placenta previa & abruptio placenta

[4] Low birth weight also adjusted for gestational age

TABLE 5: Reproductive outcomes following medical and surgical abortion

Reproductive outcomes in next (2nd) pregnancy	Primigravida N=457477	Medical termination in first pregnancy N=16702	Surgical termination in first pregnancy N=52560	RR	Medical vs Primigravida Crude and Adjusted (Adj.) Relative Risk (99% CI) [1]	Surgical vs Primigravida Crude and Adjusted (Adj.) Relative Risk (99% CI) [1]	Surgical vs Medical induced abortion Crude and Adjusted (Adj.) Relative Risk (99% CI) [1]
Live birth	355674 (77.7)	9785 (58.6)	28285 (53.8)	Crude Adj.	**0.75 (0.74, 0.77)** **0.71 (0.70, 0.73)**	**0.69 (0.69, 0.70)** **0.76 (0.75, 0.77)**	**0.92 (0.90, 0.94)** **1.44 (1.41, 1.48)**
Still birth	1406 (0.3)	57 (0.3)	151 (0.3)	Crude Adj.	1.11 (0.79, 1.57) 1.15 (0.80, 1.64)	0.93 (0.75, 1.17) 0.95 (0.73, 1.23)	0.84 (0.56, 1.26) 0.98 (0.57, 1.69)
Miscarriage	30669 (6.7)	1200 (7.2)	3723 (7.1)	Crude Adj.	1.07 (1.00, 1.15) 0.98 (0.91, 1.06)	**1.06 (1.01, 1.10)** 1.03 (0.98, 1.08)	0.99 (0.91, 1.07) **1.45 (1.30, 1.62)**
Ectopic	2939 (0.6)	120 (0.7)	599 (1.1)	Crude Adj.	1.12 (0.88, 1.42) 0.99 (0.78, 1.28)	**1.77 (1.58, 1.99)** **1.80 (1.58, 2.06)**	**1.59 (1.23, 2.05)** **1.78 (1.29, 2.45)**
Induced Abortion	66789 (14.6)	5540 (33.2)	19802 (37.7)	Crude Adj.	**2.27 (2.21, 2.34)** **3.01 (2.91, 3.12)**	**2.58 (2.54, 2.63)** **2.00 (1.96, 2.04)**	**1.14 (1.10, 1.17)** **0.44 (0.42, 0.46)**
Outcome in ongoing pregnancy[4]	N=457477	N=9842	N=28436				
Pre-Eclampsia	8649 (1.9)	316 (3.2)	688 (2.4)	Crude Adj.	**1.70 (1.47, 1.96)** 1.01 (0.86, 1.17**)**	**1.28 (1.16, 1.42)** **1.14 (1.03, 1.27)**	0.75 (0.63, 0.90) 1.12 (0.90, 1.39)
Placenta praevia	2042 (0.5)	23 (0.2)	248 (0.9)	Crude Adj.	**0.52 (0.31, 0.90)** 0.81 (0.47, 1.40)	**1.95 (1.64, 2.32)** **1.63 (1.36, 1.95)**	3.73 (2.13, 6.54) **2.23 (1.17, 4.26)**
Abruptio placentae	1770 (0.4)	40 (0.4)	160 (0.6)	Crude Adj.	1.05 (0.70, 1.58) **1.65 (1.08, 2.52)**	**1.45 (1.18, 1.80)** **1.54 (1.24, 1.91)**	1.38 (0.88, 2.18) 1.09 (0.63, 1.88)
Birth weight [2]	28735 (6.3)	697 (7.1)	2407 (8.5)	Crude	**1.13 (1.03, 1.24)**	**1.35 (1.28, 1.42)**	1.19 (1.07, 1.33)

<2500 g				Adj.	1.05 (0.94, 1.17)	**1.16 (1.08, 1.23)**	1.12 (0.97, 1.28)
Spontaneous births[4]	**N=318217[3]**	**N=6474[3]**	**N=18126[3]**				
Preterm <37 wks	21891 (6.9)	533 (8.2)	1768 (9.8)	Crude Adj.	**1.20 (1.07, 1.33)** 1.11 (0.99, 1.24)	**1.42 (1.34, 1.51)** **1.45 (1.37, 1.55)**	**1.18 (1.05, 1.34)** **1.25 (1.07, 1.45)**
Very Preterm <32 wks	4051 (1.3)	123 (1.9)	363 (2.0)	Crude Adj.	**1.49 (1.18, 1.89)** 1.25 (0.98, 1.60)	**1.57 (1.37, 1.81)** **1.62 (1.41, 1.87)**	1.05 (0.81, 1.38) 1.13 (0.81, 1.58)
Very Preterm <28 wks	1349 (0.4)	35 (0.5)	120 (0.7)	Crude Adj.	1.27 (0.82, 2.00) 0.91 (0.58, 1.44)	**1.56 (1.22, 2.00)** **1.62 (1.27, 2.07)**	1.23 (0.75, 2.01) 1.38 (0.73, 2.61)

Values are n (%) unless otherwise specified

[1] All relative risks comparing medical vs surgical have been adjusted for maternal age, year of event, Carstairs category at the previous & interpregnancy interval

[2] Low birth weight also adjusted for gestational age

[3] Only spontaneous delivery considered among live & still birth

4 All relative risks comparing primigravida vs medical/surgical have been adjusted for maternal age, year of event, Carstairs category at the ongoing pregnancy

TABLE 6: Risk of spontaneous preterm delivery following increasing number of induced abortions

	PTD < 37 weeks		PTD <32 weeks		PTD<28 weeks	
	Crude RR (99% C.I.)	Adj.RR (99% C.I.)*	Crude RR (99% CI)	Adj RR(99% CI)	Crude RR(99% CI)	Adj RR (99% CI)
1 previous abortion vs 0	**1.50 (1.41, 1.59)**	**1.47 (1.38, 1.57)**	**1.70 (1.47, 1.96)**	**1.59 (1.37, 1.84)**	**1.44 (1.09, 1.87)**	1.24 (0.94, 1.64)
2 previous abortions vs 0	**1.55 (1.32, 1.81)**	**1.51 (1.29, 1.77)**	1.48 (1.00, 2.19)	1.34 (0.91, 2.00)	**2.27 (1.31, 3.94)**	**1.89 (1.08, 3.31)**
3 previous abortions vs 0	**1.55 (1.04, 2.31)**	**1.52 (1.01, 2.27)**	1.81 (0.74, 4.46)	1.64 (0.67, 4.06)	1.36 (0.22, 8.37)	**1.12 (0.18, 6.96)**
4 previous abortions vs 0	**2.13 (1.26, 3.64)**	**2.10 (1.23, 3.59)**	**4.62 (1.91, 11.19)**	**4.27(1.76,10.37)**	**6.94 (1.95, 24.72)**	**5.96(1.65,21.37)**
2 previous abortions vs 1	1.03 (0.87, 1.22)	1.02 (0.86, 1.21)	0.87 (0.57, 1.31)	0.84 (0.56, 1.28)	1.58 (0.86, 2.89)	1.52 (0.83, 2.78)
3 previous abortions vs 2	1.00 (0.65, 1.54)	1.01 (0.66, 1.55)	1.23 (0.46, 3.27)	1.22 (0.46, 3.26)	0.60 (0.09, 3.99)	0.60 (0.09, 3.97)
4 previous abortions vs 3	1.38 (0.71, 2.68)	1.38 (0.71, 2.70)	2.55 (0.72, 9.01)	2.60 (0.74, 9.18)	5.10 (0.56, 46.78)	5.29 (0.58, 48.70)

PTD preterm delivery

Supplementary Table A

Comparison of reproductive and perinatal outcomes in the 1st pregnancy (live birth & full term) in women who had induced abortion, livebirth or miscarriage in the 2nd pregnancy

Outcome of 1st pregnancy	Outcome of second pregnancy			Crude Relative Risk (99% CI) [1]	
Live birth	Induced abortion N=30527	Live birth N=125855	Miscarriage N=22404	Induced abortion vs Live birth	Induced abortion vs Miscarriage
Pre-eclampsia	349 (1.1)	1447 (1.2)	325 (1.5)	0.99 (0.85, 1.16)	0.79 (0.65, 0.96)
Placenta previa	128 (0.4)	409 (0.3)	80 (0.4)	1.29 (0.99, 1.67)	1.17 (0.81, 1.69)
Abruptio placenta	84 (0.3)	262 (0.2)	57 (0.3)	1.32 (0.96, 1.82)	1.08 (0.70, 1.68)
Induction of labour[3]	8064 (26.4)	33225 (26.4)	6103 (27.2)	1.00 (0.97, 1.03)	0.97 (0.93, 1.01)
Low birth weight <2500[4]	972 (3.2)	3727 (3.0)	626 (2.8)	1.08 (0.98, 1.18)	1.14 (1.00, 1.30)

Values are n (%) unless otherwise specified

Reproductive outcomes following ectopic pregnancy: a national register based cohort study in Scotland

Supplemental file: STROBE Statement

Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Location within manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title & Abstract: Line 51
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract: Lines 52 - 97
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction: Lines 112 - 159
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction: Lines 161-170
Methods			
Study design	4	Present key elements of study design early in the paper	Methodology: Line 173
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods Lines 178-181
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods: Lines 178 - 207
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods: Lines 213 - 221
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods: Lines 210 - 211.
Bias	9	Describe any efforts to address potential sources of bias	The only possible source of bias could be misclassification of variables as routinely collected data are used. We think that the large dataset should

			compensate for that.
Study size	10	Explain how the study size was arrived at	All available data were included. Power calculation: lines 225 -235.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis: Lines 238-267
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis: Lines 238-267
		(*b*) Describe any methods used to examine subgroups and interactions	Methods: Lines 203 - 207
		(*c*) Explain how missing data were addressed	Methodology: Lines 152 - 159
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable.
		(*e*) Describe any sensitivity analyses	Methodology Lines 261-267
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results: Lines 176 - 177
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	The whole population was selected
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1 and 3
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 and 3
		(c) Summarise follow-up time (eg, average and total amount)	Table 1 and 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2,4,5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 4, 5
		(*b*) Report category boundaries when	Methods, Tables 2, 4, 5

		continuous variables were categorized	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results: Lines 266-7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion: Lines 341-353
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion: Lines 377-389
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion: Lines 439-449
Generalis-ability	21	Discuss the generalisability (external validity) of the study results	Discussion: Lines 363-373

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Lines 479-480

Reproductive outcomes following induced abortion: a national register based cohort study in Scotland

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000911.R2
Article Type:	Research
Date Submitted by the Author:	27-Jun-2012
Complete List of Authors:	Bhattacharya, Siladitya; University of Aberdeen, Institute of Applied Health Sciences Lowit, Alison; University of Aberdeen, Institute of Applied Health Sciences Bhattacharya, Sohinee; University of Aberdeen, Public Health Raja, Edwin Amalraj; University of Aberdeen, Medical Statistics, Dept. of Public Health Lee, Amanda; University of Aberdeen, Medical Statistics, Dept. of Public Health Mahmood, Tahir; Forth Park Hospital, Obstetrics and Gynaecology Templeton, Allan; University of Aberdeen, Institute of Applied Health Sciences
Primary Subject Heading:	Reproductive medicine, obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS, PERINATOLOGY, REPRODUCTIVE MEDICINE

Reproductive outcomes following induced abortion: a national register based cohort study in Scotland

Siladitya Bhattacharya[1], Alison Lowit[1] Sohinee Bhattacharya[1*], Edwin A Raja[1], Amanda J Lee[1], Tahir Mahmood[2], Allan Templeton[1]

[1]Division of Applied Health Sciences, University of Aberdeen
[2]Forth Park Hospital, Kirkcaldy

*Corresponding author

All correspondence to:
Sohinee Bhattacharya
Lecturer, Obstetric Epidemiology
University of Aberdeen
Dugald Baird Centre for Research on Women's Health
Aberdeen Maternity Hospital
AB25 2ZL
Tel: +44 (0)1224 438441
e-mail: sohinee.bhattacharya@abdn.ac.uk

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: The Chief Scientist Office Scotland funded the study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Abstract

Objective: To investigate reproductive outcomes in women following induced abortion (IA).

Design: Retrospective cohort study

Setting: Hospital admissions between 1981 and 2007 in Scotland.

Participants: Data were extracted on all women who had an IA, a miscarriage or a live birth from the Scottish Morbidity Records. A total of 120,033, 457,477 and 47,355 women with a documented second pregnancy following an IA, livebirth and miscarriage respectively were identified.

Outcomes: Obstetric and perinatal outcomes, especially preterm delivery in a second ongoing pregnancy following an IA were compared with those in primigravidae, as well as those who had a miscarriage or live birth in their first pregnancy. Outcomes after surgical and medical termination as well as after one or more consecutive IAs were compared.

Results: IA in a first pregnancy increased the risk of spontaneous preterm birth compared to that in primigravidae [Adjusted relative risk (Adj. RR) 1.37, 95% Confidence Interval (CI) 1.32, 1.42] or women with an initial live birth [Adj. RR 1.66, 95% CI 1.58-1.74], but not in comparison with women with a previous miscarriage [Adj. RR 0.85, 95% CI 0.79-0.91].
Surgical abortion increased the risk of spontaneous preterm birth compared to medical abortion [Adj. RR 1.25, 95% CI 1.07-1.45)]. The adjusted relative risks (95% CI) for spontaneous preterm delivery following two, three and four consecutive IAs were 0.94 (0.81-1.10), 1.06 (0.76-1.47) and 0.92 (0.53-1.61) respectively.

Conclusion: The risk of preterm birth after induced abortion is lower than that after miscarriage but higher than that in a first pregnancy or after a previous live birth. This risk is not increased further in women who undergo two or more consecutive induced abortions. Surgical abortion appears to be associated with an increased risk of spontaneous preterm birth in comparison with medical termination of pregnancy.

Background

Many women start their reproductive careers with an abortion in their first pregnancy. In 2009, 13,005 abortions were performed in Scotland with the highest rates in women aged 16-19 years [1]. What is not yet entirely clear is the effect these abortions may have on subsequent childbearing. It has been believed that infection, cervical trauma and endometrial curettage associated with induced abortion could lead to future infertility, ectopic, preterm delivery and placenta praevia, but the data from existing observational studies are mixed [2 -18] Following the legalisation of abortion in 1967, initial research on the effects of an induced abortion on subsequent pregnancies showed no evidence of an increased risk of miscarriage, preterm delivery or low birth weight[19, 20]. Much of the work in the subject has been hampered by methodological limitations; randomised controlled studies are not feasible in this context and researchers have looked to observational studies. Many of the published studies have been limited by small sample sizes, self-reported outcomes and inability to adjust for many potential confounders. A recent review [21] reported that half of the twelve relevant studies found an association between induced abortion and preterm birth as well as placenta praevia. More recently a number of large studies found no increased risk of placenta praevia, but supported an association with preterm [18, 22, 23] and very preterm delivery [24, 25] The clinical implications of this are profound as reducing the incidence of preterm delivery, with its considerable associated problems, remains one of the most significant challenges in obstetrics.

Over a quarter of induced abortions in Scotland in 2005 were repeat procedures [1] [ISD, personal communication]. While the reproductive sequalae of repeat abortions are unclear, the available literature suggests that the risk of preterm delivery is increased by multiple abortions [18, 22, 24, 26].

Changes in the technique of abortion have to be taken into account when assessing their impact on future reproduction. In 1992, 83.6% of terminations were carried out surgically, falling to 60.6% in 1998 and 40.7% in 2006, with the remainder being carried out medically [1]. A number of studies [27-29] have compared these methods in terms of safety, efficacy and short term complications but data on subsequent reproductive outcomes is scant. A recent study [30] found no difference in reproductive outcomes (ectopic, miscarriage and preterm delivery) following medically and surgically induced abortions, but was unable to adjust for known confounders such as smoking.

~~In view of the high current rates of induced abortion, it is important for women and those involved in their care to be aware of any potential associations with future reproductive outcomes.~~

The Scottish Morbidity Record (SMR) system in Scotland covers a national population and has captured data on medical and surgical abortion for many years. Over 99.3% of abortions in Scotland are carried out in NHS premises and are recorded in the SMR system. As these data are based on clinical records, any potential bias created by underreporting will be removed. The availability of this large national dataset provides an ideal opportunity to link records on abortion (SMR01) with maternity records (SMR02) in order to explore the risk of preterm delivery and other maternal and perinatal outcomes in women following one or more episodes of induced abortion. The data would also allow a meaningful comparison of outcomes following alternative forms of induced abortion (i.e. medical versus surgical).

The primary aim of this study was to investigate reproductive outcomes in women following induced abortion. In particular we wished to answer the following research questions: 1) Is an induced abortion *in a first pregnancy* associated with spontaneous preterm birth or other adverse obstetric or perinatal outcomes in the second pregnancy? 2) Is an induced abortion performed *after a singleton term first pregnancy* associated with spontaneous preterm birth or adverse obstetric or perinatal outcomes in the next pregnancy? 3) Do any of these associations differ by method of induced abortion (i.e. surgical versus medical)? 4) Is the risk of adverse obstetric or perinatal outcomes associated with increasing number of terminations?

Methods

A retrospective cohort study design was used on routinely collected data extracted from the Information and Statistics Division (ISD) database. Approval was obtained from the Privacy Advisory Committee of the National Health Service, Scotland.

Data were extracted from the ISD databases (SMR01 and 02) on women aged 15-55 years who had an induced abortion, a miscarriage, a live birth, or an ongoing pregnancy and live delivery in their first pregnancy between 1981 and 2007 followed by a second pregnancy event. Reproductive outcomes in the subsequent pregnancy of women who had an IA in their first pregnancy (exposed

cohort) were compared with those in two unexposed groups: 1) women in their second pregnancy after a miscarriage in their first pregnancy and 2) women in their second pregnancy after a live birth in their first pregnancy. In addition to these two unexposed cohorts, obstetric and perinatal outcomes in the subsequent pregnancy of women who had an IA in their first pregnancy (exposed group), were also compared with those women in their first pregnancy.

To explore outcomes following early pregnancy loss after an initial livebirth, data were extracted on all women (15-55 years of age) who had an induced abortion, a miscarriage, or a live birth, in their second pregnancy (following a live birth in their first pregnancy) between 1981 and 2007 from the ISD databases (SMR01 and 02) and followed up to identify a third pregnancy event. Reproductive, obstetric and perinatal outcomes in women who had an IA after a singleton term first pregnancy (exposed group), were compared with those in two unexposed groups: 1) women in their third pregnancy following a singleton term delivery in the first pregnancy and a miscarriage in the second pregnancy and 2) women in their third pregnancy following two singleton term deliveries

Women treated by different methods of induced abortion (surgical or medical) in a first pregnancy were compared in terms of reproductive, obstetric and perinatal outcomes. Finally, to answer research question 4, reproductive and perinatal outcomes were compared between women who had 1, 2, 3 and 4 previous consecutive induced abortions and women with no previous abortions. Each group of women was independent of the others – for example women who had 3 abortions were excluded from the group with 2 abortions. For each analysis, except research question 4, the women were matched on parity as the risk of adverse obstetric outcomes is dependent on parity with primiparous women suffering the highest risk.

Data extracted

The following variables were identified by matching SMR01 and SMR02 datasets between the years 1981 and 2007.

Demographic details: Age at pregnancy events, smoking status, and social class (assessed using Carstairs category of deprivation) in the exposed group were compared with each of the 3 unexposed cohorts

Induced abortion details: estimated gestation and method of termination (medical or surgical or both) were recorded for the exposed group. Reproductive outcomes: miscarriage, abortion, livebirth, ectopic, stillbirth in the exposed group were compared with the unexposed cohorts. Obstetric and perinatal outcomes: The incidence of pre-eclampsia, placenta praevia, placental abruption, preterm delivery, very preterm delivery, low birth weight and the mode of delivery in the exposed cohort were compared with each of the 3 unexposed cohorts. Spontaneous delivery rates (including live and stillbirth) were calculated after excluding women who had induced labour and elective (planned) caesarean section.

Socioeconomic status was assessed using the Carstairs index [31] which was divided into quintiles for analysis.

Power Calculation

Given the number of sub-groups in the analysis coupled with multiple outcomes, a global sample size calculation was not feasible. Preliminary enquiries with ISD suggested that we could identify at least 260,000 terminations (1981-2007), of which 30% (n=69,000) were estimated to have had a subsequent live birth and 25.5% (n=66,223) were induced abortions in a first pregnancy.

Using a 1:1 ratio of women with induced abortions in a first pregnancy (exposed cohort) and unexposed women, we anticipated having over 90% power, at the two-sided 5% significance level, to detect a difference of 0.5% or more in the chances of a preterm birth (ie, an odds ratio of 1.09) assuming that the prevalence of live births in the unexposed group was 6%.

Statistical Analysis

In the absence of an ideal comparison group for women with a prior abortion, we used 3 unexposed cohorts which could increase the chance of false positive associations (type I error). To help minimise this, we used a stringent p-value of ≤0.01 to denote statistical significance throughout the statistical analyses.

A generalised linear model was used with Poisson family and robust variance estimator to ascertain the relationship between exposure (first pregnancy induced abortion) and various reproductive outcomes (still birth, miscarriage, ectopic and induced abortion), maternal and perinatal outcomes (pre-eclampsia, placenta-previa, abruption placenta) after adjusting for potential confounders (maternal

age, year of delivery, smoking & carstairs at relevant pregnancy). For the outcome of induction of labour, pre-eclampsia, placenta previa and placental abruption were also entered into the model. Similarly, the outcome low birth weight was also adjusted for gestational age. Stata version 11 was used for the analysis and a stringent p-value of ≤0.01 was used to denote statistical significance throughout.

As smoking data were not routinely collected in the maternity database (SMR02) before 1992, and rarely recorded for women having an induced abortion or miscarriage. Thus self-reported smoking status, collected at antenatal booking visit, though available for some women was non-randomly missing for a high percentage of women. This sometimes led to non-convergence of the statistical models. Therefore, a sensitivity analysis was carried out by re-running all of the multivariate models excluding the smoking variable to determine if the overall effect sizes remained of similar magnitude. This was found to be so.

Results

Demographic characteristics of women who had an abortion in their first pregnancy were compared with those who had either a live birth or a miscarriage in their first pregnancy and with primigravida women (Table 1). Women with a previous induced abortion were significantly older, more socially deprived and more likely to be smokers than primigravida women or those who had a live birth or a miscarriage in a previous pregnancy.

Table 2 presents reproductive outcomes in a subsequent pregnancy following IA, livebirth and miscarriage in the first pregnancy. As Table 2 shows, women with an IA in the first pregnancy were more at risk of having a still birth or an induced abortion in the second pregnancy as compared with an initial livebirth. Compared to those who had an initial miscarriage, women who had an IA in their first pregnancy were less likely to have a subsequent miscarriage or ectopic pregnancy, but more likely to have another induced abortion.

Perinatal outcomes in the next ongoing pregnancy following IA are also compared with those in primigravida and women who have had a livebirth or miscarriage in Table 2. Compared with women having a previous livebirth, women who had an induced abortion were at higher risk of pre-eclampsia, abruptio placenta, induction of labour, spontaneous preterm and very preterm delivery (<32weeks) extremely preterm (< 28 weeks) and delivery of a low birth weight baby (<2500 g) but not placenta praevia.

In comparison with women with a previous miscarriage, a history of IA was associated with a lower risk of developing pre-eclampsia and spontaneous preterm and very preterm delivery. Risks of pre-eclampsia, placental abruption (but not placenta praevia), delivery of a low birth weight baby and spontaneous preterm, very preterm and extremely preterm birth were significantly higher following IA than in primigravid women. The risk of pre-eclampsia in women with a previous IA was higher than in primigravid women but lower than in women with a previous miscarriage (Table 2).

The demographic characteristics of women who had a livebirth in a first pregnancy and then went on to have induced abortion, live birth or a miscarriage in their second pregnancy are shown in Table 3. Women with an induced abortion in their second pregnancy were younger, belonged to a more deprived social group and were more likely to be smokers than women who had a live birth in their second pregnancy. Compared to women who had a miscarriage in their second pregnancy, women with a previous induced abortion were older, belonged to more deprived social classes and were more likely to smoke.

As Table 4 shows, IA in the second pregnancy was associated with a higher risk of an ectopic or an induced abortion in the third pregnancy as compared with an initial livebirth. The risk of miscarriage in a third pregnancy was lower in women who had an IA in a second pregnancy, but the risks of another induced abortion were higher than in women with a previous miscarriage.

Compared to women with two previous livebirths, women with a livebirth followed by an IA were more likely to have pre-eclampsia, placenta praevia, induced labour, low birthweight and spontaneous preterm, very preterm and extremely preterm birth (Table 4). Women with an IA in a second pregnancy were not at any significantly higher risk of perinatal complications in comparison with women with a previous miscarriage.

In records where the method of IA was clearly recorded, 52,560 women were noted to have had surgical and 16,702, medical abortions. As Table 5 shows, reproductive outcomes were comparable in the two groups except for a lower risk of a second induced abortion following surgical termination of pregnancy. The adjusted relative risk of miscarriage, ectopic pregnancy, placenta praevia and spontaneous preterm delivery (<37 weeks) were significantly higher after surgical

termination. In comparison with primigravid women i.e. no previous abortion, women with a medical abortion had an increased risk of placental abruption, but not spontaneous preterm, very preterm or extremely preterm delivery. In contrast, women with a surgical abortion had higher risks of all three types of spontaneous preterm delivery. They also had an increased risk of preeclampsia, placenta praevia, abruption and low birthweight babies. More women had repeat abortion following surgical termination of pregnancy, and fewer went on to have a livebirth in comparison with primigravid women and those who had medical terminations.

Table 6 summarises the risk of spontaneous preterm delivery in subsequent pregnancies following one or more consecutive IAs in comparison to those with no previous abortions (primigravid women). The adjusted relative risks of spontaneous preterm birth, (< 37 weeks) was incrementally higher in women undergoing 1, 2, 3 and 4 induced abortions. The adjusted relative risk of spontaneous very preterm delivery (< 32 weeks) was higher after 1 and 4 induced abortions. while the adjusted relative risk of spontaneous extremely preterm delivery (<28weeks) was higher following 2 and 4 previous induced abortions. Additional induced abortions were not associated with increased adjusted relative risks of any type of spontaneous preterm birth.

Discussion

Principal findings

Our results suggest that women who had an induced abortion in the first pregnancy were more at risk of maternal and perinatal risks in comparison to women with a previous live birth. Compared to an initial miscarriage, an induced abortion in a first pregnancy was associated with a higher subsequent risk of miscarriage or ectopic pregnancy, induced abortion and pre-eclampsia. Women with a previous induced abortion face increased risks of antepartum haemorrhage and spontaneous preterm birth than women in their first pregnancy.

A livebirth prior to an IA does not appear to be associated with reduced perinatal complications in women who are at higher risk of spontaneous preterm birth than primigravida. Surgical termination appears to be associated with a higher chance of spontaneous preterm birth than medical IA. There does not appear to be a dose dependent effect of IA on future adverse perinatal outcomes.

Women with three or four consecutive induced abortions were not at significantly higher risk of spontaneous preterm birth in comparison with women who have had one termination of pregnancy.

Strengths

To our knowledge this is the largest population based study of reproductive outcomes following an induced abortion. Registry based previous studies reporting preterm birth rates as an outcome have been unable to discriminate between spontaneous and induced preterm delivery; this is one of the first papers to be able to calculate and report spontaneous preterm birth rates after induced abortion.

We have acknowledged changes in clinical practice over the years during which data were collected and have adjusted for year of pregnancy in the regression models. The choice of an appropriate comparison group to women with a history of induced abortion is problematic. Women who are pregnant again after having undergone an induced abortion in a previous (first) pregnancy are gravida 2 and parity 0. It is impossible to control for both gravidity and parity unless the unexposed cohort have had a prior pregnancy which did not lead to a delivery. Other comparison groups can be either women in their first ongoing pregnancies (gravidity 1 parity 0), or in their second ongoing pregnancies after a previous delivery (gravidity 2 parity 1). We feel that our strategy comparing the exposed cohort to all three of the above groups adds validity to our results.

Limitations

The main limitations of this study stem from unrecorded and missing data in relation to certain potential confounding factors within the dataset. For example, smoking data were only available for 50% of women; data on body mass index were unavailable while data on gestational age at termination was missing in the majority of cases. The actual method of termination (medical versus surgical) was unrecorded in around 25% of all cases, while a large number of women appeared to have both medical as well as surgical treatment. Parity number was less reliable in the early years of data collection. This may reflect problems with coding and could potentially affect the quality of our results. In addition, the analysis of such a large population based dataset has the capacity to produce statistically significant differences which may or may not be clinically relevant,

although this has been minimised by our use of a stringent 1% significance level throughout.

Defining an ideal reference group is a challenge in studies exploring outcomes after induced abortion. While we have partially addressed this issue by using more than one unexposed cohort, our data do not allow us to adjust for potential differences in pregnancy intentions between groups, which can impact on antenatal care and perinatal outcomes.

Unrecorded data relating to key potential confounders cannot exclude the possibility that some associations are not explained by abortion itself but by special circumstances of women seeking abortion which also increases their risk of complications in pregnancy. We ran a separate analysis to identify previous pregnancy complications in women who either had an induced abortion, miscarriage or livebirth in a second pregnancy. As supplementary Table A shows, induced abortion in the second pregnancy was not significantly associated with increased relative risk (99% confidence interval) of preeclampsia, placenta praevia, placental abruption and low birthweight respectively compared to either livebirth [0.99 (0.85, 1.16); 1.29 (0.99, 1.67) 1.32 (0.96, 1.82) 1.08 (0.98, 1.18)] or miscarriage [0.79 (0.65, 0.96) 1.17 (0.81, 1.69) 1.08 (0.70, 1.68) 1.14 (1.00, 1.30)].

Comparison with previous studies

The association between induced abortion and preterm birth found in this study is consistent with previously published work [32]. Two recent meta-analyses suggest that women who have had an IA are at higher risk of preterm birth in subsequent pregnancies [33, 34]. Our study shows that after adjustment women with a previous abortion have an increased chance of a subsequent preterm birth and very pre-term birth compared with primigravidae or those who have had a previous live birth, but at no significantly greater risk compared to women who have had a previous miscarriage. Women who had a live birth before an induced abortion are more likely to have a preterm birth compared to women with two previous live births.

Our results did not suggest a signficant increased risk of miscarriage after an induced abortion which is in keeping with a review of literature [21]. In contrast, Sun (2003)[35] demonstrated an association between surgical abortion and miscarriage in a subsequent pregnancy. Literature on the association between IA and miscarriage or ectopic pregnancy is sparse and conflicting. The increased risk of having a second termination following

induced abortion in a first pregnancy highlighted in our study has been reported elsewhere [36-38]. While women who had an abortion were more likely to have a subsequent abortion, but they may also be more likely to have an unintended pregnancy. This should be seen a potential risk factor which should be explored in future studies.

Available literature suggests there is an association between IA and placenta previa [39, 40], but no association with abruptio placenta [41, 42]. This study found that women in their second pregnancy after an initial induced abortion in the first were at higher odds of both placenta previa and abruptio placenta, women in their third pregnancy after an induced abortion in their second pregnancy had higher odds of placenta previa, but not abruptio placenta. Published evidence supports a decreased risk of pre-eclampsia after an IA [43, 44]. Our results suggest a risk of developing preeclampsia which is on par with primigravid women, but lower than women with a previous miscarriage. The reasons for these associations are unclear and hence any explanations can only be speculative. Problems with placental position and function could occur due to disruption of the endometrium by vigorous curettage. The quality of placental function in a previous pregnancy could influence susceptibility to future preeclampsia.

Since the introduction of medical abortion there has been much speculation about the rival merits of medical and surgical techniques, especially in terms of future reproductive outcomes. Analysis of Danish data has failed to demonstrate a difference in key outcomes such as preterm birth between medical and surgical abortion, but this study was unable to identify spontaneous versus induced preterm birth [30]. With our ability to identify spontaneous PTBs, we have shown a clear association with surgical abortion. However, since we were unable to adjust for gestational age, we cannot rule out the possibility that surgical abortions may have been performed at a more advanced stage of pregnancy requiring a greater degree of cervical dilatation – thus leading to future preterm labour. Our results are supported by a recent publication showing that the risk of preterm birth after one or more surgical abortions is higher than after medical abortion and comparable to that in primigravid women [11].

A dose dependent relationship between the number of IAs and future PTB has been shown in a number of previous studies [32]. The results of our analysis do not

support this. Given our inability to adjust for a number of potential confounders, this needs to be investigated further.

Our data suggest that medical and surgical terminations may impact differently on future reproductive outcomes - with a higher risk of spontaneous preterm birth after surgery. We were unable to disentangle the separate effects of repeated medical and surgical abortion due to a relative paucity of numbers.
A recent publication [11] found an increased risk of premature delivery following multiple surgical, but not first trimester, medical induced abortions. While this could reflect the effect of repeated surgical trauma to the cervix, this needs further exploration in future studies with long term periods of follow up.

A key challenge in studying health sequalae after induced abortion is to deal with potential differences in pregnancy intentions between comparison groups. While women who had an abortion were more likely to have a subsequent abortion, they may also be more likely to have an unintended pregnancy, which needs to be acknowledged as a potential risk factor in future studies.

Conclusions

Induced abortion in a first pregnancy is associated with a higher risk of spontaneous preterm birth in a subsequent pregnancy in comparison with primigravid women, but not women with a previous miscarriage. A successful pregnancy leading to a livebirth prior to an induced abortion does not appear to ameliorate this risk while more than one abortion does not significantly increase it. Surgical abortion appears to be associated with an increased risk of spontaneous very preterm birth in comparison with medical termination of pregnancy. The results of this study should help provide women as well as health professionals with accurate information to inform clinical decision making and tailor antenatal care to address women's risk profiles.

AT conceived the idea for the study. SB was the Principal Investigator. He designed the study along with SohB, AT, ALee and TM, led the funding application, managed the project, interpreted the results and wrote the first draft of the paper. ALo cleaned the data and performed some of the initial analyses. SohB co-wrote the funding application, facilitated data manipulation, interpreted the results and helped to draft the paper. EAR performed the statistical analysis and interpreted the results with input from ALee. All authors commented on, and contributed to the final draft of the paper.

Acknowledgements

We thank staff at ISD Scotland for extraction of data from the Scottish Morbidity Records Database and Margery Heath for secretarial assistance.

Funding

The Chief Scientist Office Scotland funded the study. The views expressed are those of the authors and not the funding body.

Contributorship

AT conceived the idea for the study. SB was the Principal Investigator. He designed the study along with SohB, AT, ALee and TM, led the funding application, managed the project, interpreted the results and wrote the first draft of the paper. ALo cleaned the data and performed some of the initial analyses. SohB co-wrote the funding application, facilitated data manipulation, interpreted the results and helped to draft the paper. EAR performed the statistical analysis and interpreted the results with input from ALee. All authors commented on, and contributed to the final draft of the paper.

References

1. Available at: http://www.isdscotland.org/isd/CCC_FirstPage.jsp-.

2. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiol Rev* 1993;15(2):414-43.

3. Calhoun BC, Shadigian E, Rooney B. Cost consequences of induced abortion as an attributable risk for preterm birth and impact on informed consent. *J Reprod Med* 2007; Oct;52(10):929-37.

4. Chen A, Yuan W, Meirik O, et al. Mifepristone-induced early abortion and outcome of subsequent wanted pregnancy. *Am J Epidemiol* 2004; Jul 15;160(2):110-7.

5. de Haas I, Harlow BL, Cramer DW, et al. Spontaneous preterm birth: a case-control study. *Am J Obstet Gynecol* 1991; Nov;165(5 Pt 1):1290-6.

6. Foix-L'Helias L, Blondel B. Changes in risk factors of preterm delivery in France between 1981 and 1995. *Paediatr Perinat Epidemiol* 2000; Oct;14(4):314-23.

7. Freak-Poli R, Chan A, Tucker G, et al. Previous abortion and risk of pre-term birth: a population study. *J Maternal-Fetal & Neonatal Med* 2009;22(1):1-7.

8. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. *Lancet* 2008; Jan 5;371(9606):75-84.

9. Lang JM, Lieberman E, Cohen A. A comparison of risk factors for preterm labor and term small-for-gestational-age birth. *Epidemiology* 1996; Jul;7(4):369-76.

10. Lekea-Karanika V, Tzoumaka-Bakoula C, Golding J. Previous obstetric history and subsequent preterm delivery in Greece. *Eur J Obstet Gynecol Reprod Biol* 1990; Nov;37(2):99-109.

11. Liao H, Wei Q, Duan L, et al. Repeated medical abortions and the risk of preterm birth in the subsequent pregnancy. *Arch Gynecol Obstet* 2011; Sep;284(3):579-86.

12. Martius JA, Steck T, Oehler MK, et al. Risk factors associated with preterm (<37+0 weeks) and early preterm birth (<32+0 weeks): univariate and multivariate analysis of 106,345 singleton births from the 1994 statewide perinatal survey of Bavaria. *European Journal of Obstetrics Gynecology and Reproductive Biology* 1998;80(2):183,184-189.

13. Pickering RM, Deeks JJ. Risks of delivery during the 20th to the 36th week of gestation. *Int J Epidemiol* 1991; Jun;20(2):456-66.

14. Reime B, Schucking BA, Wenzlaff P. Reproductive outcomes in adolescents who had a previous birth or an induced abortion compared to adolescents' first pregnancies. *BMC Pregnancy Childbirth* 2008; Jan 31;8:4.

15. Voigt M, Olbertz D, Fusch C, et al. The influence of previous pregnancy terminations, miscarriages and still-births on the incidence of babies with low birth weight and premature births as well as a somatic classification of newborns. *Z Geburtshilfe Neonatol* 2008; Feb;212(1):5-12.

16. Watson LF, Rayner JA, King J, et al. Modelling sequence of prior pregnancies on subsequent risk of very preterm birth. *Paediatr Perinat Epidemiol* 2010; Sep;24(5):416-23.

17. Winer N, Resche-Rigon M, Morin C, et al. Is induced abortion with misoprostol a risk factor for late abortion or preterm delivery in subsequent pregnancies?. *Eur J Obstet Gynecol Reprod Biol* 2009; Jul;145(1):53-6.

18. Zhou W, Sorensen HT, Olsen J. Induced abortion and subsequent pregnancy duration. *Obstet Gynecol* 1999; Dec;94(6):948-53.

19. Atrash HK, Hogue CJ. The effect of pregnancy termination on future reproduction. *Baillieres Clin Obstet Gynaecol* 1990; Jun;4(2):391-405.

20. Hogue CJ. Impact of abortion on subsequent fecundity. *Clinics in Obstetrics & Gynaecology* 1986;13(1):95,96-103.

21. Thorp JM, Hartmann KE, Shadigian E. Long-term physical and psychological health consequences of induced abortion: review of the evidence. *Obstet Gynecol Survey* 2002; 58;1(67):79.

22. Ancel PY, Lelong N, Papiernik E, et al. History of induced abortion as a risk factor for preterm birth in European countries: results from the EUROPOP survey. *Hum Reprod* 2004;19(3):734-40.

23. Raatikainen K, Heiskanen N, Heinonen S. Induced abortion: not an independent risk factor for pregnancy outcome, but a challenge for health counseling. *Ann Epidemiol* 2006; Aug;16(8):587-92.

24. Moreau C, Kaminski M, Ancel PY, et al. Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study. *BJOG* 2005; Apr;112(4):430-7.

25. Zhou W, Nielsen GL, Larsen H, et al.Induced abortion and placenta complications in the subsequent pregnancy. *Acta Obstet Gynecol Scand* 2001; Dec;80(12):1115-20.

26. Henriet L, Kaminski M. Impact of induced abortions on subsequent pregnancy outcome: the 1995 French national perinatal survey. *BJOG* 2001; Oct;108(10):1036-42.

27. Henshaw RC, Naji SA, Russsell IT, et al. A comparison of medical abortion (using mifepristone and gemeprost) with surgical vacuum aspiration: efficacy and early medical sequelae. *Human Reproduction* 1994;9(11):2167,2168-2171.

28. Ashok PW, Kidd A, Flett GM, et al. A randomized colmparison of medical abortin and surgical vacuum aspiration at 10-13 weeks gestation. *Human Reproduction* 2002;17(1):92,93-98.

29. Rorbye C, Norgaard M, Nilas L. Medical versus surgical abortion efficacy, complications and leave of absence compared in a partly randomized study. *Contraception 2004* 2004;70(5):393,394-399.

30. Virk J, Zhang J, Olsen J. Medical abortion and the risk of subsequent adverse pregnancy outcomes. *N Engl J Med* 2007; Aug 16;357(7):648-53.

31. Carstairs V MR. Deprivation and Health in Scotland 1991;.

32. Lowit A, Bhattacharya S. Obstetric performance following an induced abortion. *Best Practice & Research - Clinical Obstetrics & Gynaecology* 2010;24(5):667,668-82.

33. Shah PS, Zao J. Induced termination of pregnancy and low birth weight and preterm birth: a systemic review and meta-analysis. *BJOG* 2009;116:1425-42.

34. Swingle HM, Colaizy TT, Zimmerman MB, et al. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analysis. *J Reprod Med* 2009;54:95-108.

35. Sun Y, Che Y, Ershang G, et al. Induced abortion and risk of subsequent miscarriage. *Int J Epidemiol* 2003; 32;(449):454.

36. Heikinheimo O, Gissler M, Suhonen S. Age, parity, history of abortion and contraceptive choices affect the risk of repeat abortions. *Contraception 2008* 2008;:149,150-154.

37. Prager SW, Steinauer JE, Foster DF, et al. Risk factors for repeat elective abortion. *American Journal of Obstetrics & Gynecology* 2007;197:e1-575,576-e6.

38. Rowlands S. More than one abortion. *Joural Fam Plann Reprod Health Care* 2007;33(3):155,156-158.

39. Ananth CV, Smulian JC, Vintzileos AM. The effect of placenta previa on neonatal mortality: a population-based study in the United States, 1989 through 1997. *Am J Obstet Gynecol* 2003; May;188(5):1299-304.

40. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta abruption in an Asian population. *Reproductive Sciences* 2007;14(1):59-65.

41. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta previa in an Asian population. *Int J Gynecol & Obstet* 2007;97:26-30.

42. Zhu QX, Gao ES, Chen AM, et al. Mifepristone-induced abortion and placenta complications in subsequent pregnancy. *Hum Reprod* 2009;24(2):315-9.

43. Eras JL, Saftlas AF, Triche E, et al. Abortion and its effect on risk of pre-eclampsia and transient hypertension. *Epidemiology* 2000;11:36-43.

44. Trogstad L, Magnus P, Skjaerven R, et al. Previous abortions and risk of pre-eclampsia. *Int J Epidemiology* 2008;37:1333-40.

TABLE 1: Demographic characteristics at first pregnancy of women who had induced abortion, livebirth or miscarriage in their first pregnancy

		Outcome in first pregnancy				
		Induced abortion N=120,033	**Live birth N=457,477**	**p-value**	**Miscarriage N=47,355**	**p-value**
Mean Age (SD)		24.68 (7.56)	24.89 (5.11)	<0.001	26.26 (6.13)	<0.001
Carstairs Category [1,2]	1	17265 (17.1)	79705 (18.0)	<0.001	8403 (18.8)	<0.001
	2	18538 (18.3)	81661 (18.4)		8206 (18.4)	
	3	19530 (19.3)	84559 (19.1)		8794 (19.7)	
	4	21135 (20.9)	92504 (20.9)		9426 (21.1)	
	5	24615 (24.4)	105313 (23.7)		9788 (21.9)	
Smoking status[2]	Never	1014 (42.3)	112744 (48.4)	<0.001	4892 (39.8)	<0.001
	Current	676 (28.2)	72182 (31.0)		2044 (16.6)	
	Former	85 (3.5)	22140 (9.5)		533 (4.3)	
	Not known	622 (26.0)	26088 (11.2)		4818 (39.2)	
	Total	2397	233154		12287	
	Missing	117636 (98.0)	224323 (49.0)		35068 (74.1)	
Interpregnancy interval in Weeks	Median (IQR)	165 (78, 321)	139 (95, 213)	<0.001	65 (47, 104)	<0.001

Values are n (%) unless otherwise specified

[1] Carstairs categories 1 = least deprived, 5 = most deprived

[2] Percentage based on available information for each group

TABLE 2: Reproductive and perinatal outcomes following induced abortion, miscarriage or live birth in first pregnancy

Outcome of 2nd pregnancy	**Outcome in First pregnancy**				**Crude and Adjusted (Adj.) Relative Risk (99% CI)** [1]		
	Induced abortion N=120033	**Live birth N=457477**	**Miscarriage N=47355**		**Induced abortion vs Live birth**	**Induced abortion vs Miscarriage**	
Live birth	67336 (56.1)	355674 (77.7)	36479 (77.0)		Crude 0.72 (0.71, 0.73) Adj. 0.74 (0.73, 0.74)	Crude 0.72 (0.72, 0.73) Adj. 0.69 (0.69, 0.70)	
Still birth	409 (0.34)	1406 (0.31)	247 (0.52)		Crude 1.11 (0.96, 1.28) Adj. 1.06 (0.91, 1.24)	Crude 0.65 (0.53, 0.80) Adj. **0.58(0.46, 0.74)**	
Miscarriage	7965 (6.6)	30669 (6.7)	6197 (13.1)		Crude 0.99 (0.96, 1.02) Adj. **1.05(1.01, 1.08)**	Crude 0.51 (0.49, 0.53) Adj. **0.56(0.54, 0.59)**	
Ectopic	1115 (0.9)	2939 (0.6)	499 (1.1)		Crude 1.45 (1.32, 1.58) Adj. **1.36(1.23, 1.50)**	Crude 0.88 (0.77, 1.01) Adj. **0.83(0.71, 0.97)**	
Induced abortion	43208 (36.0)	66789 (14.6)	3933 (8.3)		Crude 2.47 (2.43, 2.50) Adj. **2.30(2.27, 2.33)**	Crude 4.33 (4.16, 4.51) Adj. **4.64(4.44, 4.85)**	
Outcomes in ongoing pregnancies	**N=67745**	**N=357080**	**N=36726**	**Primigravida N=457477**			**Induced abortion vs Primigravida**
Pre-eclampsia	1583 (2.3)	2982 (0.8)	922 (2.5)	8649 (1.9)	Crude 2.80 (2.58, 3.03) Adj. **2.42 (2.21, 2.65)**	Crude 0.93 (0.84, 1.03) Adj. **0.83 (0.73, 0.94)**	Crude 1.24 (1.15, 1.32) Adj. **1.26 (1.17, 1.35)**
Placentaprevia	385 (0.6)	1919 (0.5)	289 (0.8)	2042 (0.5)	Crude 1.06 (0.92, 1.22) Adj. 1.09 (0.93, 1.28)	Crude 0.72 (0.59, 0.88) Adj. 0.79 (0.62, 1.01)	Crude 1.27 (1.10, 1.47) Adj. 1.05 (0.91, 1.22)
Abruptio placenta	339 (0.5)	1197 (0.3)	173 (0.5)	1770 (0.4)	Crude 1.49 (1.27, 1.75) Adj. **1.49 (1.25, 1.77)**	Crude 1.06 (0.84, 1.35) Adj. 1.00 (0.76, 1.32)	Crude 1.30 (1.11, 1.51) Adj. **1.28 (1.10, 1.50)**
Induction of labour[2]	18044 (26.6)	69482 (19.5)	10347 (28.2)	120080 (26.3)	Crude 1.37 (1.34, 1.39) Adj. **1.33 (1.30, 1.35)**	Crude 0.95 (0.92, 0.97) Adj. 0.98 (0.95, 1.01)	Crude 1.01 (1.00, 1.03) Adj. 1.00 (0.99, 1.02)
Low birth weight <2500g[3]	5385 (8.0)	16309 (4.6)	3101 (8.5)	28735 (6.3)	Crude 1.74 (1.67, 1.81) Adj. **1.24 (1.17, 1.31)**	Crude 0.94 (0.89, 1.00) Adj. 0.96 (0.90, 1.03)	Crude 1.27 (1.22, 1.31) Adj. **1.08 (1.04, 1.13)**
Outcomes in spontaneous births	**N= 45656**	**N=255220**	**N=23751**	**N=318217**			
Spontaneous preterm birth <37 weeks	4224 (9.3)	13453 (5.3)	2376 (10.0)	21891 (6.9)	Crude 1.76 (1.68, 1.83) Adj. **1.66 (1.58, 1.74)**	Crude 0.92 (0.86, 0.97) Adj. **0.85 (0.79, 0.91)**	Crude 1.35 (1.29, 1.40) Adj. **1.37 (1.32, 1.42)**
Spontaneous very preterm birth <34 weeks	1512 (3.3)	3994 (1.6)	865 (3.6)	7154 (2.3)	Crude 2.12 (1.96, 2.29) Adj. **2.00 (1.83, 2.18)**	Crude 0.90 (0.82, 1.01) Adj. **0.86 (0.76, 0.98)**	Crude 1.47 (1.37, 1.58) Adj. **1.52 (1.41, 1.63)**

Values are n (%) unless otherwise specified

[1] Adjusted for maternal age, year of delivery, Carstairs at first pregnancy & interpregnancy interval.

[2] Further adjusted for pre-eclampsia, placenta previa & abruptio placenta.

[3] Low birth weight also adjusted for gestational age.

TABLE 3: Demographic characteristics of women who had induced abortion, livebirth or miscarriage after an initial livebirth

		Outcome in second pregnancy following an initial livebirth				
		Induced abortion N=30527	**Live birth N=125855**	**p-value**	**Miscarriage N=22404**	**p-value**
Mean Age (SD)		26.04 (5.85)	26.15 (4.68)	<0.001	28.41 (5.42)	0.001
Carstairs Category[1,2]	1	3523 (12.8)	20264 (16.5)	<0.001	4498 (20.9)	<0.001
	2	4304 (15.6)	21985 (17.9)		4079 (18.9)	
	3	5186 (18.8)	23425 (19.0)		4312 (20.0)	
	4	6243 (22.6)	25979 (21.1)		4447 (20.6)	
	5	8370 (30.3)	31395 (25.5)		4235 (19.6)	
Smoking status[2]	Never	393 (39.7)	32464 (48.5)	<0.001	3165 (46.1)	0.001
	Current	313 (31.6)	20658 (30.9)		1169 (17.0)	
	Former	43 (4.3)	5359 (8.0)		282 (4.1)	
	Not known	241 (24.3)	8482 (12.7)		2243 (32.7)	
	Total	990	66963		6859	
	Missing	29537 96.8)	58892 (46.8)		15545 (69.4)	
Interpregnancy interval	Median(IQR)	108 (61, 209)	152 (96, 256)	<0.001	60 (48, 87)	<0.001

Values are n (%) unless otherwise specified

[1] Carstairs categories 1 = least deprived, 5 = most deprived

[2] Percentage based on available information for each group

TABLE 4: Reproductive and perinatal outcomes in women who had induced abortion, livebirth or miscarriage following a livebirth in the first pregnancy

Outcome of 3rd pregnancy	Outcome of second pregnancy			Crude and Adjusted (Adj.) Relative Risk (99% CI) [1]	
	Induced abortion N=30527	Live birth N=125855	Miscarriage N=22404	Induced abortion vs Live birth	Induced abortion vs Miscarriage
Live birth	18562 (60.8)	85014 (67.5)	17745 (79.2)	Crude 0.90 (0.89, 0.91) Adj. 0.88 (0.87, 0.89)	Crude 0.77 (0.76, 0.78) Adj. 0.77 (0.76, 0.78)
Still birth	84 (0.3)	426 (0.3)	69 (0.3)	Crude 0.81 (0.60, 1.11) Adj. 0.76 (0.55, 1.06)	Crude 0.89 (0.59, 1.36) Adj. 0.86 (0.54, 1.37)
Miscarriage	2005 (6.6)	8778 (7.0)	2869 (12.8)	Crude 0.94 (0.89, 1.00) Adj. **0.93 (0.88, 1.00)**	Crude 0.51 (0.48, 0.55) Adj. **0.67 (0.62, 0.72)**
Ectopic	339 (1.1)	1064 (0.9)	181 (0.8)	Crude 1.31 (1.12, 1.54) Adj. **1.31 (1.11, 1.56)**	Crude 1.38 (1.09, 1.74) Adj. 1.16 (0.90, 1.50)
Induced abortion	9537 (31.2)	30573 (24.3)	1540 (6.9)	Crude 1.29 (1.25, 1.32) Adj. **1.33 (1.30, 1.37)**	Crude 4.55 (4.25, 4.86) Adj. **4.37 (4.06, 4.70)**
Outcomes in ongoing pregnancies	**Induced Abortion N=18646**	**Live birth N=85440**	**Miscarriage N=17814**	**Crude and Adjusted (Adj.) Relative Risk (99% CI) [2]**	
Pre-eclampsia	144 (0.8)	567 (0.7)	165 (0.9)	Crude 1.16 (0.92, 1.48) Adj. **1.40 (1.10, 1.79)**	Crude 0.83 (0.62, 1.12) Adj. 0.91 (0.66, 1.27)
Placenta previa	183 (1.0)	473 (0.6)	133 (0.8)	Crude 1.77 (1.42, 2.22) Adj. **1.78 (1.40, 2.25)**	Crude 1.32 (0.98, 1.76) Adj. 1.34 (0.97, 1.84)
Abruptio placenta	91 (0.5)	325 (0.4)	66 (0.4)	Crude 1.28 (0.95, 1.74) Adj. 1.28 (0.93, 1.77)	Crude 1.32 (0.87, 2.00) Adj. 1.32 (0.83, 2.10)
Induction of labour[3]	4298 (23.1)	18239 (21.4)	3968 (22.3)	Crude 1.08 (1.04, 1.12) Adj. **1.11 (1.07, 1.16)**	Crude 1.03 (0.98, 1.09) Adj. 1.01 (0.96, 1.07)
Low birth weight <2500[4]	1086 (5.8)	3905 (4.6)	784 (4.4)	Crude 1.28 (1.17, 1.39) Adj. **1.36 (1.21, 1.51)**	Crude 1.32 (1.17, 1.49) Adj. 1.04 (0.90, 1.21)
Outcomes in spontaneous births	**Induced abortion N=12868**	**Live birth N=59220**	**Miscarriage N=12056**		
Spontaneous preterm birth <37 weeks	859 (6.7)	3035 (5.1)	644 (5.3)	Crude 1.30 (1.18, 1.43) Adj. **1.27 (1.14, 1.40)**	Crude 1.25 (1.10, 1.42) Adj. 1.14 (0.99, 1.32)
Spontaneous very preterm birth <34 weeks	282 (2.2)	929 (1.6)	189 (1.6)	Crude 1.40 (1.17, 1.66) Adj. **1.36 (1.13, 1.64)**	Crude 1.40 (1.10, 1.78) Adj. **1.33 (1.01, 1.74)**

Values are n (%) unless otherwise specified

[1] Adjusted for age, year of delivery, carstairs at second pregnancy & interpregnancy interval

[2] Adjusted for maternal age, year of pregnancy, Carstairs category at second pregnancy & interpregnancy interval

[3] Further adjusted for pre-eclampsia, placenta previa & abruptio placenta

[4] Low birth weight also adjusted for gestational age

TABLE 5: Reproductive outcomes following medical and surgical abortion

Reproductive outcomes in next (2nd) pregnancy	Surgical termination in first pregnancy N=52560	Medical termination in first pregnancy N=16702	Surgical vs Medical induced abortion Crude and Adjusted (Adj.) Relative Risk (99% CI) [1]
Live birth	28285 (53.8)	9785 (58.6)	Crude 0.92 (0.90, 0.94) Adj. 1.44 (1.41, 1.48)
Still birth	151 (0.3)	57 (0.3)	Crude 0.84 (0.56, 1.26) Adj. 0.98 (0.57, 1.69)
Miscarriage	3723 (7.1)	1200 (7.2)	Crude 0.99 (0.91, 1.07) Adj. **1.45 (1.30, 1.62)**
Ectopic	599 (1.1)	120 (0.7)	Crude 1.59 (1.23, 2.05) Adj. **1.78 (1.29, 2.45)**
Induced Abortion	19802 (37.7)	5540 (33.2)	Crude 1.14 (1.10, 1.17) Adj. **0.44 (0.42, 0.46)**
Outcome in ongoing pregnancy	N=28, 436	N=9842	
Pre-Eclampsia	688 (2.4)	316 (3.2)	Crude 0.75 (0.63, 0.90) Adj. 1.12 (0.90, 1.39)
Placenta praevia	248 (0.9)	23 (0.2)	Crude 3.73 (2.13, 6.54) Adj. **2.23 (1.17, 4.26)**
Abruptio placentae	160 (0.6)	40 (0.4)	Crude 1.38 (0.88, 2.18) Adj. 1.09 (0.63, 1.88)
Birth weight [2] <2500 g	2407 (8.5)	697 (7.1)	Crude 1.19 (1.07, 1.33) Adj. 1.12 (0.97, 1.28)
Spontaneous births	**N=18126**[3]	**N=6474**[3]	
Preterm <37 wks	1768 (9.8)	533 (8.2)	Crude 1.18 (1.05, 1.34) Adj. **1.25 (1.07, 1.45)**
Very Preterm <34 wks	633 (3.5)	217 (3.4)	Crude 1.04 (0.86, 1.27) Adj. 1.09 (0.84, 1.40)

Values are n (%) unless otherwise specified

[1] All relative risks have been adjusted for maternal age, year of event, Carstairs category at the previous & interpregnancy interval

[2] Low birth weight also adjusted for gestational age

[3] Only spontaneous delivery considered among live & still birth

TABLE 6: Comparisons of perinatal outcomes following one or more induced abortions

	No of consecutive previous induced abortions				Crude and Adjusted[1] (Adj.) Relative Risks for perinatal outcomes after 2, 3 and 4 abortions compared to 1 abortion (99% confidence Interval)					
	1 N=25348	**2 N=3622**	**3 N=565**	**4 N=225**	**2 vs 1[4]**		**3 vs 1[4]**		**4 vs 1[4]**	
Low birth weight <2500g [2, 3]	2188 (8.6)	325 (9.0)	54 (9.6)	20 (8.9)	Crude Adj.	1.04 (0.90, 1.20) 0.92 (0.77, 1.11)	Crude Adj.	1.11 (0.79, 1.55) 0.99 (0.73, 1.34)	Crude Adj.	1.03 (0.59, 1.79) 0.54 (0.25, 1.16)
Induction of labour	6919 (27.3)	1005 (27.8)	170 (30.1)	72 (32.0)	Crude Adj.	1.02 (0.94, 1.09) 1.02 (0.95, 1.10)	Crude Adj.	1.10 (0.93, 1.30) 1.11 (0.94, 1.31)	Crude Adj.	1.17 (0.91, 1.51) 1.20 (0.93, 1.55)
	N=16275	**N=2285**	**N=347**	**N=136**						
Spontaneous preterm birth <37 weeks	1676 (10.3)	243 (10.6)	37 (10.7)	20 (14.7)	Crude Adj.	1.03 (0.88, 1.22) 0.94 (0.81, 1.10)	Crude Adj.	1.04 (0.69, 1.55) 1.06 (0.76, 1.47)	Crude Adj.	1.43 (0.84, 2.44) 0.92 (0.53, 1.61)
Spontaneous preterm birth <34weeks	613 (3.8)	87 (3.8)	17 (4.9)	9 (6.6)	Crude Adj.	1.01 (0.76, 1.35) 0.96 (0.71, 1.28)	Crude Adj.	1.30 (0.70, 2.41) 1.14 (0.60, 2.14)	Crude Adj.	1.76 (0.76, 4.05) 1.61 (0.69, 3.72)

Values are n (%) unless otherwise specified

[1] All relative risks have been adjusted for maternal age, year of event, Carstairs category & interpregnancy interval.

[2] Low birth weight also adjusted for gestational age

[3] Percentage calculated based on number available in the group

[4] Comparison group is women with 1 IA

Reproductive outcomes following induced abortion: a national register based cohort study in Scotland

Siladitya Bhattacharya[1], Alison Lowit[1] Sohinee Bhattacharya[1*], Edwin A Raja[1], Amanda J Lee[1], Tahir Mahmood[2], Allan Templeton[1]

[1]Division of Applied Health Sciences, University of Aberdeen
[2]Forth Park Hospital, Kirkcaldy

*Corresponding author

All correspondence to:
Sohinee Bhattacharya
Lecturer, Obstetric Epidemiology
University of Aberdeen
Dugald Baird Centre for Research on Women's Health
Aberdeen Maternity Hospital
AB25 2ZL
Tel: +44 (0)1224 438441
e-mail: sohinee.bhattacharya@abdn.ac.uk

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: The Chief Scientist Office Scotland funded the study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Abstract

Background

The impact of induced abortions on subsequent childbearing is of major importance to women. Some published studies have shown a link between induced abortion and subsequent preterm birth but existing studies have been largely unable to disentangle spontaneous and induced preterm delivery. The primary aim of this study was to investigate reproductive outcomes in women following induced abortion.

Methods

Data were extracted on all women (aged 15-55 years) who had an induced abortion, a miscarriage, a livebirth, or an ongoing pregnancy and live delivery in their first pregnancy recorded between 1981 and 2007 in the Scottish Morbidity Records databases. Obstetric and perinatal outcomes in a second ongoing pregnancy following an induced abortion were compared with those in primigravidae, as well as those who had had a miscarriage or livebirth in their first pregnancy. Spontaneous preterm birth rates were also compared in women following surgical and medical termination as well as after one or more consecutive induced abortions.

Findings

A total of 120,033, 457,477 and 47,355 women with a documented second pregnancy following an initial induced abortion (IA), livebirth and miscarriage respectively between 1981 and 2007 were identified. Data from first pregnancies from the 457,477 women who had an initial livebirth constituted a third unexposed cohort of primigravidae. Women who underwent an initial induced abortion were younger and more socially deprived than those who had a livebirth or a miscarriage ($p<0.001$). The livebirth group contained the highest proportion of current smokers, followed by the abortion group.

Women with an induced abortion in a first pregnancy had a higher risk of spontaneous preterm live birth in the next pregnancy than women in their first pregnancies [Adjusted relative risk (Adj. RR) 1.37, 99% Confidence Interval (CI) 1.32, 1.43] or women who had a livebirth in their first pregnancy [Adj. RR 1.66, 99% CI 1.58-1.74], but a lower risk in comparison with women with a previous miscarriage [Adj. RR 0.85, 99% CI 0.79-0.92]

Following an initial induced abortion, women were more likely to be diagnosed with placental abruption than either primigravidae [Adj. RR 1.28, 99% CI 1.10-

1.50] or women with a previous livebirth [Adj. RR 1.49, 99% CI 1.25-1.77]. The risk of pre-eclampia was higher in women with previous induced abortion in comparison with primigravidae [Adj. RR 1.26, 99% CI 1.17-1.35] or women with a previous livebirth [Adj. RR 2.42, 99% CI 2.21- 2.65].

In comparison with women who had an initial miscarriage, women with an IA in their first pregnancy were less likely to have a subsequent miscarriage [Adj. RR 0.56, 99% CI 0.54-0.590] or ectopic pregnancy [Adj. RR 0.83, 95% CI 0.71-0.97] but more likely to have a second induced abortion [Adj. RR 4.64, 99% CI 4.44-4.85]. They were less prone to develop pre-eclampsia [Adj. RR 0.83, 99% CI 0.73-0.94] in their next ongoing pregnancy.

Surgical abortion was associated with a higher chance of spontaneous preterm birth in the next ongoing pregnancy than medical abortion [Adj. RR 1.25, 99% CI 1.07-1.45)]. Compared with primigravid women, the risk of spontaneous preterm delivery was higher after surgical (Adj. RR 1.45 (1.37, 1.55) but not medical abortion (1.11 (0.99, 1.24). The adjusted relative risks (99% CI) for spontaneous preterm birth in the next ongoing pregnancy following two, three and four consecutive IAs in comparison with a single IA were 1.02 (0.86-1.21), 1.01 (0.66-1.55) and 1.38 (0.71-2.70) respectively.

Interpretation

Induced abortion in a first pregnancy is associated with a higher risk of spontaneous pretermbirth in a subsequent pregnancy than that in primigravidae or women with a previous livebirth, but is lower than that observed in women with an initial miscarriage. This is the first study to show that surgical, but not medical abortion appears to be associated with an increased risk of spontaneous preterm birth.

Background

Many women start their reproductive careers with an abortion in their first pregnancy. In 2009, 13,005 abortions were performed in Scotland with the highest rates in women aged 16-19 years [1]. What is not yet entirely clear is the effect these abortions may have on subsequent childbearing. It has been believed that infection, cervical trauma and endometrial curettage associated with induced abortion could lead to future infertility, ectopic, preterm delivery and placenta praevia, but the data from existing observational studies are mixed [2 -18] Following the legalisation of abortion in 1967, initial research on the effects of an induced abortion on subsequent pregnancies showed no evidence of an increased risk of miscarriage, preterm delivery or low birth weight[19, 20]. Much of the work in the subject has been hampered by methodological limitations; randomised controlled studies are not feasible in this context and researchers have looked to observational studies. Many of the published studies have been limited by small sample sizes, self-reported outcomes and inability to adjust for many potential confounders. A recent review [21] reported that half of the twelve relevant studies found an association between induced abortion and preterm birth as well as placenta praevia. More recently a number of large studies found no increased risk of placenta praevia, but supported an association with preterm [18, 22, 23] and very preterm delivery [24, 25] The clinical implications of this are profound as reducing the incidence of preterm delivery, with its considerable associated problems, remains one of the most significant challenges in obstetrics.

Over a quarter of induced abortions in Scotland in 2005 were repeat procedures [1] [ISD, personal communication]. While the reproductive sequalae of repeat abortions are unclear, the available literature suggests that the risk of preterm delivery is increased by multiple abortions [18, 22, 24, 26].

Changes in the technique of abortion have to be taken into account when assessing their impact on future reproduction. In 1992, 83.6% of terminations were carried out surgically, falling to 60.6% in 1998 and 40.7% in 2006, with the remainder being carried out medically [1]. A number of studies [27-29] have compared these methods in terms of safety, efficacy and short term complications but data on subsequent reproductive outcomes is scant. A recent study [30] found no difference in reproductive outcomes (ectopic, miscarriage and preterm delivery) following medically and surgically induced abortions, but was unable to adjust for known confounders such as smoking.

~~In view of the high current rates of induced abortion, it is important for women and those involved in their care to be aware of any potential associations with future reproductive outcomes.~~

The Scottish Morbidity Record (SMR) system in Scotland covers a national population and has captured data on medical and surgical abortion for many years. Over 99.3% of abortions in Scotland are carried out in NHS premises and are recorded in the SMR system. As these data are based on clinical records, any potential bias created by underreporting will be removed. The availability of this large national dataset provides an ideal opportunity to link records on abortion (SMR01) with maternity records (SMR02) in order to explore the risk of preterm delivery and other maternal and perinatal outcomes in women following one or more episodes of induced abortion. The data would also allow a meaningful comparison of outcomes following alternative forms of induced abortion (i.e. medical versus surgical).

The primary aim of this study was to investigate reproductive outcomes in women following induced abortion. In particular we wished to answer the following research questions: 1) Is an induced abortion *in a first pregnancy* associated with spontaneous preterm birth or other adverse obstetric or perinatal outcomes in the second pregnancy? 2) Is an induced abortion performed *after a singleton term first pregnancy* associated with spontaneous preterm birth or adverse obstetric or perinatal outcomes in the next pregnancy? 3) Do any of these associations differ by method of induced abortion (i.e. surgical versus medical)? 4) Is the risk of adverse obstetric or perinatal outcomes associated with increasing number of terminations?

Methods

A retrospective cohort study design was used on routinely collected data extracted from the Information and Statistics Division (ISD) database. Approval was obtained from the Privacy Advisory Committee of the National Health Service, Scotland.

Data were extracted from the ISD databases (SMR01 and 02) on women aged 15-55 years who had an induced abortion, a miscarriage, a live birth, or an ongoing pregnancy and live delivery in their first pregnancy between 1981 and 2007 followed by a second pregnancy event. Reproductive outcomes in the subsequent pregnancy of women who had an IA in their first pregnancy (exposed

cohort) were compared with those in two unexposed groups: 1) women in their second pregnancy after a miscarriage in their first pregnancy and 2) women in their second pregnancy after a live birth in their first pregnancy. In addition to these two unexposed cohorts, obstetric and perinatal outcomes in the subsequent pregnancy of women who had an IA in their first pregnancy (exposed group), were also compared with those women in their first pregnancy.

To explore outcomes following early pregnancy loss after an initial livebirth, data were extracted on all women (15-55 years of age) who had an induced abortion, a miscarriage, or a live birth, in their second pregnancy (following a live birth in their first pregnancy) between 1981 and 2007 from the ISD databases (SMR01 and 02) and followed up to identify a third pregnancy event. Reproductive, obstetric and perinatal outcomes in women who had an IA after a singleton term first pregnancy (exposed group), were compared with those in two unexposed groups: 1) women in their third pregnancy following a singleton term delivery in the first pregnancy and a miscarriage in the second pregnancy and 2) women in their third pregnancy following two singleton term deliveries

Women treated by different methods of induced abortion (surgical or medical) in a first pregnancy were compared in terms of reproductive, obstetric and perinatal outcomes. Finally, to answer research question 4, reproductive and perinatal outcomes were compared between women who had 1, 2, 3 and 4 previous consecutive induced abortions and women with no previous abortions. Each group of women was independent of the others – for example women who had 3 abortions were excluded from the group with 2 abortions. For each analysis, except research question 4, the women were matched on parity as the risk of adverse obstetric outcomes is dependent on parity with primiparous women suffering the highest risk.

Data extracted

The following variables were identified by matching SMR01 and SMR02 datasets between the years 1981 and 2007.

Demographic details: Age at pregnancy events, smoking status, and social class (assessed using Carstairs category of deprivation) in the exposed group were compared with each of the 3 unexposed cohorts

Induced abortion details: estimated gestation and method of termination (medical or surgical or both) were recorded for the exposed group. Reproductive outcomes: miscarriage, abortion, livebirth, ectopic, stillbirth in the exposed group were compared with the unexposed cohorts. Obstetric and perinatal outcomes: The incidence of pre-eclampsia, placenta praevia, placental abruption, preterm delivery, very preterm delivery, low birth weight and the mode of delivery in the exposed cohort were compared with each of the 3 unexposed cohorts. Spontaneous delivery rates (including live and stillbirth) were calculated after excluding women who had induced labour and elective (planned) caesarean section.

Socioeconomic status was assessed using the Carstairs index [31] which was divided into quintiles for analysis.

Power Calculation

Given the number of sub-groups in the analysis coupled with multiple outcomes, a global sample size calculation was not feasible. Preliminary enquiries with ISD suggested that we could identify at least 260,000 terminations (1981-2007), of which 30% (n=69,000) were estimated to have had a subsequent live birth and 25.5% (n=66,223) were induced abortions in a first pregnancy.

Using a 1:1 ratio of women with induced abortions in a first pregnancy (exposed cohort) and unexposed women, we anticipated having over 90% power, at the two-sided 5% significance level, to detect a difference of 0.5% or more in the chances of a preterm birth (ie, an odds ratio of 1.09) assuming that the prevalence of live births in the unexposed group was 6%.

Statistical Analysis

In the absence of an ideal comparison group for women with a prior abortion, we used 3 unexposed cohorts which could increase the chance of false positive associations (type I error). To help minimise this, we used a stringent p-value of ≤0.01 to denote statistical significance throughout the statistical analyses.

A generalised linear model was used with Poisson family and robust variance estimator to ascertain the relationship between exposure (first pregnancy induced abortion) and various reproductive outcomes (still birth, miscarriage, ectopic and induced abortion), maternal and perinatal outcomes (pre-eclampsia, placenta-previa, abruption placenta) after adjusting for potential confounders (maternal

age, year of delivery, smoking & carstairs at relevant pregnancy). For the outcome of induction of labour, pre-eclampsia, placenta previa and placental abruption were also entered into the model. Similarly, the outcome low birth weight was also adjusted for gestational age. Stata version 11 was used for the analysis and a stringent p-value of ≤0.01 was used to denote statistical significance throughout.

As smoking data were not routinely collected in the maternity database (SMR02) before 1992, and rarely recorded for women having an induced abortion or miscarriage. Thus self-reported smoking status, collected at antenatal booking visit, though available for some women was non-randomly missing for a high percentage of women. This sometimes led to non-convergence of the statistical models. Therefore, a sensitivity analysis was carried out by re-running all of the multivariate models excluding the smoking variable to determine if the overall effect sizes remained of similar magnitude. This was found to be so.

Results

Demographic characteristics of women who had an abortion in their first pregnancy were compared with those who had either a live birth or a miscarriage in their first pregnancy and with primigravida women (Table 1). Women with a previous induced abortion were significantly older, more socially deprived and more likely to be smokers than primigravida women or those who had a live birth or a miscarriage in a previous pregnancy.

Table 2 presents reproductive outcomes in a subsequent pregnancy following IA, livebirth and miscarriage in the first pregnancy. As Table 2 shows, women with an IA in the first pregnancy were more at risk of having a still birth or an induced abortion in the second pregnancy as compared with an initial livebirth. Compared to those who had an initial miscarriage, women who had an IA in their first pregnancy were less likely to have a subsequent miscarriage or ectopic pregnancy, but more likely to have another induced abortion.

Perinatal outcomes in the next ongoing pregnancy following IA are also compared with those in primigravida and women who have had a livebirth or miscarriage in Table 2. Compared with women having a previous livebirth, women who had an induced abortion were at higher risk of pre-eclampsia, abruptio placenta, induction of labour, spontaneous preterm and very preterm delivery (<32weeks) extremely preterm (< 28 weeks) and delivery of a low birth weight baby (<2500 g) but not placenta praevia.

In comparison with women with a previous miscarriage, a history of IA was associated with a lower risk of developing pre-eclampsia and spontaneous preterm and very preterm delivery. Risks of pre-eclampsia, placental abruption (but not placenta praevia), delivery of a low birth weight baby and spontaneous preterm, very preterm and extremely preterm birth were significantly higher following IA than in primigravid women. The risk of pre-eclampsia in women with a previous IA was higher than in primigravid women but lower than in women with a previous miscarriage (Table 2).

The demographic characteristics of women who had a livebirth in a first pregnancy and then went on to have induced abortion, live birth or a miscarriage in their second pregnancy are shown in Table 3. Women with an induced abortion in their second pregnancy were younger, belonged to a more deprived social group and were more likely to be smokers than women who had a live birth in their second pregnancy. Compared to women who had a miscarriage in their second pregnancy, women with a previous induced abortion were older, belonged to more deprived social classes and were more likely to smoke.

As Table 4 shows, IA in the second pregnancy was associated with a higher risk of an ectopic or an induced abortion in the third pregnancy as compared with an initial livebirth. The risk of miscarriage in a third pregnancy was lower in women who had an IA in a second pregnancy, but the risks of another induced abortion were higher than in women with a previous miscarriage.

Compared to women with two previous livebirths, women with a livebirth followed by an IA were more likely to have pre-eclampsia, placenta praevia, induced labour, low birthweight and spontaneous preterm, very preterm and extremely preterm birth (Table 4). Women with an IA in a second pregnancy were not at any significantly higher risk of perinatal complications in comparison with women with a previous miscarriage.

In records where the method of IA was clearly recorded, 52,560 women were noted to have had surgical and 16,702, medical abortions. As Table 5 shows, reproductive outcomes were comparable in the two groups except for a lower risk of a second induced abortion following surgical termination of pregnancy. The adjusted relative risk of miscarriage, ectopic pregnancy, placenta praevia and spontaneous preterm delivery (<37 weeks) were significantly higher after surgical

termination. In comparison with primigravid women i.e. no previous abortion, women with a medical abortion had an increased risk of placental abruption, but not spontaneous preterm, very preterm or extremely preterm delivery. In contrast, women with a surgical abortion had higher risks of all three types of spontaneous preterm delivery. They also had an increased risk of preeclampsia, placenta praevia, abruption and low birthweight babies. More women had repeat abortion following surgical termination of pregnancy, and fewer went on to have a livebirth in comparison with primigravid women and those who had medical terminations.

Table 6 summarises the risk of spontaneous preterm delivery in subsequent pregnancies following one or more consecutive IAs in comparison to those with no previous abortions (primigravid women). The adjusted relative risks of spontaneous preterm birth, (< 37 weeks) was incrementally higher in women undergoing 1, 2, 3 and 4 induced abortions. The adjusted relative risk of spontaneous very preterm delivery (< 32 weeks) was higher after 1 and 4 induced abortions. while the adjusted relative risk of spontaneous extremely preterm delivery (<28weeks) was higher following 2 and 4 previous induced abortions. Additional induced abortions were not associated with increased adjusted relative risks of any type of spontaneous preterm birth.

Discussion

Principal findings

Our results suggest that women who had an induced abortion in the first pregnancy were more at risk of maternal and perinatal risks in comparison to women with a previous live birth. Compared to an initial miscarriage, an induced abortion in a first pregnancy was associated with a higher subsequent risk of miscarriage or ectopic pregnancy, induced abortion and pre-eclampsia. Women with a previous induced abortion face increased risks of antepartum haemorrhage and spontaneous preterm birth than women in their first pregnancy.

A livebirth prior to an IA does not appear to be associated with reduced perinatal complications in women who are at higher risk of spontaneous preterm birth than primigravida. Surgical termination appears to be associated with a higher chance of spontaneous preterm birth than medical IA. There does not appear to be a dose dependent effect of IA on future adverse perinatal outcomes.

Women with three or four consecutive induced abortions were not at significantly higher risk of spontaneous preterm birth in comparison with women who have had one termination of pregnancy.

Strengths

To our knowledge this is the largest population based study of reproductive outcomes following an induced abortion. Registry based previous studies reporting preterm birth rates as an outcome have been unable to discriminate between spontaneous and induced preterm delivery; this is one of the first papers to be able to calculate and report spontaneous preterm birth rates after induced abortion.

We have acknowledged changes in clinical practice over the years during which data were collected and have adjusted for year of pregnancy in the regression models. The choice of an appropriate comparison group to women with a history of induced abortion is problematic. Women who are pregnant again after having undergone an induced abortion in a previous (first) pregnancy are gravida 2 and parity 0. It is impossible to control for both gravidity and parity unless the unexposed cohort have had a prior pregnancy which did not lead to a delivery. Other comparison groups can be either women in their first ongoing pregnancies (gravidity 1 parity 0), or in their second ongoing pregnancies after a previous delivery (gravidity 2 parity 1). We feel that our strategy comparing the exposed cohort to all three of the above groups adds validity to our results.

Limitations

The main limitations of this study stem from unrecorded and missing data in relation to certain potential confounding factors within the dataset. For example, smoking data were only available for 50% of women; data on body mass index were unavailable while data on gestational age at termination was missing in the majority of cases. The actual method of termination (medical versus surgical) was unrecorded in around 25% of all cases, while a large number of women appeared to have both medical as well as surgical treatment. Parity number was less reliable in the early years of data collection. This may reflect problems with coding and could potentially affect the quality of our results. In addition, the analysis of such a large population based dataset has the capacity to produce statistically significant differences which may or may not be clinically relevant,

although this has been minimised by our use of a stringent 1% significance level throughout.

Defining an ideal reference group is a challenge in studies exploring outcomes after induced abortion. While we have partially addressed this issue by using more than one unexposed cohort, our data do not allow us to adjust for potential differences in pregnancy intentions between groups, which can impact on antenatal care and perinatal outcomes.

Unrecorded data relating to key potential confounders cannot exclude the possibility that some associations are not explained by abortion itself but by special circumstances of women seeking abortion which also increases their risk of complications in pregnancy. We ran a separate analysis to identify previous pregnancy complications in women who either had an induced abortion, miscarriage or livebirth in a second pregnancy. As supplementary Table A shows, induced abortion in the second pregnancy was not significantly associated with increased relative risk (99% confidence interval) of preeclampsia, placenta praevia, placental abruption and low birthweight respectively compared to either livebirth [0.99 (0.85, 1.16); 1.29 (0.99, 1.67) 1.32 (0.96, 1.82) 1.08 (0.98, 1.18)] or miscarriage [0.79 (0.65, 0.96) 1.17 (0.81, 1.69) 1.08 (0.70, 1.68) 1.14 (1.00, 1.30)].

Comparison with previous studies

The association between induced abortion and preterm birth found in this study is consistent with previously published work [32]. Two recent meta-analyses suggest that women who have had an IA are at higher risk of preterm birth in subsequent pregnancies [33, 34]. Our study shows that after adjustment women with a previous abortion have an increased chance of a subsequent preterm birth and very pre-term birth compared with primigravidae or those who have had a previous live birth, but at no significantly greater risk compared to women who have had a previous miscarriage. Women who had a live birth before an induced abortion are more likely to have a preterm birth compared to women with two previous live births.

Our results did not suggest a signficant increased risk of miscarriage after an induced abortion which is in keeping with a review of literature [21]. In contrast, Sun (2003)[35] demonstrated an association between surgical abortion and miscarriage in a subsequent pregnancy. Literature on the association between IA and miscarriage or ectopic pregnancy is sparse and conflicting. The increased risk of having a second termination following

induced abortion in a first pregnancy highlighted in our study has been reported elsewhere [36-38]. While women who had an abortion were more likely to have a subsequent abortion, but they may also be more likely to have an unintended pregnancy. This should be seen a potential risk factor which should be explored in future studies.

Available literature suggests there is an association between IA and placenta previa [39, 40], but no association with abruptio placenta [41, 42]. This study found that women in their second pregnancy after an initial induced abortion in the first were at higher odds of both placenta previa and abruptio placenta, women in their third pregnancy after an induced abortion in their second pregnancy had higher odds of placenta previa, but not abruptio placenta. Published evidence supports a decreased risk of pre-eclampsia after an IA [43, 44]. Our results suggest a risk of developing preeclampsia which is on par with primigravid women, but lower than women with a previous miscarriage. The reasons for these associations are unclear and hence any explanations can only be speculative. Problems with placental position and function could occur due to disruption of the endometrium by vigorous curettage. The quality of placental function in a previous pregnancy could influence susceptibility to future preeclampsia.

Since the introduction of medical abortion there has been much speculation about the rival merits of medical and surgical techniques, especially in terms of future reproductive outcomes. Analysis of Danish data has failed to demonstrate a difference in key outcomes such as preterm birth between medical and surgical abortion, but this study was unable to identify spontaneous versus induced preterm birth [30]. With our ability to identify spontaneous PTBs, we have shown a clear association with surgical abortion. However, since we were unable to adjust for gestational age, we cannot rule out the possibility that surgical abortions may have been performed at a more advanced stage of pregnancy requiring a greater degree of cervical dilatation – thus leading to future preterm labour. Our results are supported by a recent publication showing that the risk of preterm birth after one or more surgical abortions is higher than after medical abortion and comparable to that in primigravid women [11].

A dose dependent relationship between the number of IAs and future PTB has been shown in a number of previous studies [32]. The results of our analysis do not

support this. Given our inability to adjust for a number of potential confounders, this needs to be investigated further.

Our data suggest that medical and surgical terminations may impact differently on future reproductive outcomes - with a higher risk of spontaneous preterm birth after surgery. We were unable to disentangle the separate effects of repeated medical and surgical abortion due to a relative paucity of numbers.
A recent publication [11] found an increased risk of premature delivery following multiple surgical, but not first trimester, medical induced abortions. While this could reflect the effect of repeated surgical trauma to the cervix, this needs further exploration in future studies with long term periods of follow up.

A key challenge in studying health sequalae after induced abortion is to deal with potential differences in pregnancy intentions between comparison groups. While women who had an abortion were more likely to have a subsequent abortion, they may also be more likely to have an unintended pregnancy, which needs to be acknowledged as a potential risk factor in future studies.

Conclusions

Induced abortion in a first pregnancy is associated with a higher risk of spontaneous preterm birth in a subsequent pregnancy in comparison with primigravid women, but not women with a previous miscarriage. A successful pregnancy leading to a livebirth prior to an induced abortion does not appear to ameliorate this risk while more than one abortion does not significantly increase it. Surgical abortion appears to be associated with an increased risk of spontaneous very preterm birth in comparison with medical termination of pregnancy. The results of this study should help provide women as well as health professionals with accurate information to inform clinical decision making and tailor antenatal care to address women's risk profiles.

AT conceived the idea for the study. SB was the Principal Investigator. He designed the study along with SohB, AT, ALee and TM, led the funding application, managed the project, interpreted the results and wrote the first draft of the paper. ALo cleaned the data and performed some of the initial analyses. SohB co-wrote the funding application, facilitated data manipulation, interpreted the results and helped to draft the paper. EAR performed the statistical analysis and interpreted the results with input from ALee. All authors commented on, and contributed to the final draft of the paper.

Acknowledgements

We thank staff at ISD Scotland for extraction of data from the Scottish Morbidity Records Database and Margery Heath for secretarial assistance.

Funding

The Chief Scientist Office Scotland funded the study. The views expressed are those of the authors and not the funding body.

References

1. Available at: http://www.isdscotland.org/isd/CCC_FirstPage.jsp-.

2. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiol Rev* 1993;15(2):414-43.

3. Calhoun BC, Shadigian E, Rooney B. Cost consequences of induced abortion as an attributable risk for preterm birth and impact on informed consent. *J Reprod Med* 2007; Oct;52(10):929-37.

4. Chen A, Yuan W, Meirik O, Wang X, Wu SZ, Zhou L, et al. Mifepristone-induced early abortion and outcome of subsequent wanted pregnancy. *Am J Epidemiol* 2004; Jul 15;160(2):110-7.

5. de Haas I, Harlow BL, Cramer DW, Frigoletto FD,Jr. Spontaneous preterm birth: a case-control study. *Am J Obstet Gynecol* 1991; Nov;165(5 Pt 1):1290-6.

6. Foix-L'Helias L, Blondel B. Changes in risk factors of preterm delivery in France between 1981 and 1995. *Paediatr Perinat Epidemiol* 2000; Oct;14(4):314-23.

7. Freak-Poli R, Chan A, Tucker G, et al. Previous abortion and risk of pre-term birth: a population study. *J Maternal-Fetal & Neonatal Med* 2009;22(1):1-7.

8. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008; Jan 5;371(9606):75-84.

9. Lang JM, Lieberman E, Cohen A. A comparison of risk factors for preterm labor and term small-for-gestational-age birth. *Epidemiology* 1996; Jul;7(4):369-76.

10. Lekea-Karanika V, Tzoumaka-Bakoula C, Golding J. Previous obstetric history and subsequent preterm delivery in Greece. *Eur J Obstet Gynecol Reprod Biol* 1990; Nov;37(2):99-109.

11. Liao H, Wei Q, Duan L, Ge J, Zhou Y, Zeng W. Repeated medical abortions and the risk of preterm birth in the subsequent pregnancy. *Arch Gynecol Obstet* 2011; Sep;284(3):579-86.

12. Martius JA, Steck T, Oehler MK, Wulf KH. Risk factors associated with preterm (<37+0 weeks) and early preterm birth (<32+0 weeks): univariate and multivariate analysis of 106,345 singleton births from the 1994 statewide perinatal survey of Bavaria. *European Journal of Obstetrics Gynecology and Reproductive Biology* 1998;80(2):183,184-189.

13. Pickering RM, Deeks JJ. Risks of delivery during the 20th to the 36th week of gestation. *Int J Epidemiol* 1991; Jun;20(2):456-66.

14. Reime B, Schucking BA, Wenzlaff P. Reproductive outcomes in adolescents who had a previous birth or an induced abortion compared to adolescents' first pregnancies. *BMC Pregnancy Childbirth* 2008; Jan 31;8:4.

15. Voigt M, Olbertz D, Fusch C, Krafczyk D, Briese V, Schneider KT. The influence of previous pregnancy terminations, miscarriages and still-births on the incidence of babies with low birth weight and premature births as well as a somatic classification of newborns. *Z Geburtshilfe Neonatol* 2008; Feb;212(1):5-12.

16. Watson LF, Rayner JA, King J, Jolley D, Forster D, Lumley J. Modelling sequence of prior pregnancies on subsequent risk of very preterm birth. *Paediatr Perinat Epidemiol* 2010; Sep;24(5):416-23.

17. Winer N, Resche-Rigon M, Morin C, Ville Y, Rozenberg P. Is induced abortion with misoprostol a risk factor for late abortion or preterm delivery in subsequent pregnancies?. *Eur J Obstet Gynecol Reprod Biol* 2009; Jul;145(1):53-6.

18. Zhou W, Sorensen HT, Olsen J. Induced abortion and subsequent pregnancy duration. *Obstet Gynecol* 1999; Dec;94(6):948-53.

19. Atrash HK, Hogue CJ. The effect of pregnancy termination on future reproduction. *Baillieres Clin Obstet Gynaecol* 1990; Jun;4(2):391-405.

20. Hogue CJ. Impact of abortion on subsequent fecundity. *Clinics in Obstetrics & Gynaecology* 1986;13(1):95,96-103.

21. Thorp JM, Hartmann KE, Shadigian E. Long-term physical and psychological health consequences of induced abortion: review of the evidence. *Obstet Gynecol* Survey 2002; 58;1(67):79.

22. Ancel PY, Lelong N, Papiernik E, et al. History of induced abortion as a risk factor for preterm birth in European countries: results from the EUROPOP survey. *Hum Reprod* 2004;19(3):734-40.

23. Raatikainen K, Heiskanen N, Heinonen S. Induced abortion: not an independent risk factor for pregnancy outcome, but a challenge for health counseling. *Ann Epidemiol* 2006; Aug;16(8):587-92.

24. Moreau C, Kaminski M, Ancel PY, Bouyer J, Escande B, Thiriez G, et al. Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study. *BJOG* 2005; Apr;112(4):430-7.

25. Zhou W, Nielsen GL, Larsen H, Olsen J. Induced abortion and placenta complications in the subsequent pregnancy. *Acta Obstet Gynecol Scand* 2001; Dec;80(12):1115-20.

26. Henriet L, Kaminski M. Impact of induced abortions on subsequent pregnancy outcome: the 1995 French national perinatal survey. *BJOG* 2001; Oct;108(10):1036-42.

27. Henshaw RC, Naji SA, Russsell IT, Templeton A. A comparison of medical abortion (using mifepristone and gemeprost) with surgical vacuum aspiration: efficacy and early medical sequelae. *Human Reproduction* 1994;9(11):2167,2168-2171.

28. Ashok PW, Kidd A, Flett GM, Fitzmaurice A, Graham W, Templeton A. A randomized colmparison of medical abortin and surgical vacuum aspiration at 10-13 weeks gestation. *Human Reproduction* 2002;17(1):92,93-98.

29. Rorbye C, Norgaard M, Nilas L. Medical versus surgical abortion efficacy, complications and leave of absence compared in a partly randomized study. *Contraception 2004* 2004;70(5):393,394-399.

30. Virk J, Zhang J, Olsen J. Medical abortion and the risk of subsequent adverse pregnancy outcomes. *N Engl J Med* 2007; Aug 16;357(7):648-53.

31. Carstairs V MR. Deprivation and Health in Scotland 1991;.

32. Lowit A, Bhattacharya S. Obstetric performance following an induced abortion. *Best Practice & Research - Clinical Obstetrics & Gynaecology* 2010;24(5):667,668-82.

33. Shah PS, Zao J. Induced termination of pregnancy and low birth weight and preterm birth: a systemic review and meta-analysis. *BJOG* 2009;116:1425-42.

34. Swingle HM, Colaizy TT, Zimmerman MB, et al. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analysis. *J Reprod Med* 2009;54:95-108.

35. Sun Y, Che Y, Ershang G, et al. Induced abortion and risk of subsequent miscarriage. *Int J Epidemiol* 2003; 32;(449):454.

36. Heikinheimo O, Gissler M, Suhonen S. Age, parity, history of abortion and contraceptive choices affect the risk of repeat abortions. *Contraception 2008* 2008;:149,150-154.

37. Prager SW, Steinauer JE, Foster DF, Darney PD, Drey EA. Risk factors for repeat elective abortion. *American Journal of Obstetrics & Gynecology* 2007;197:e1-575,576-e6.

38. Rowlands S. More than one abortion. *Joural Fam Plann Reprod Health Care* 2007;33(3):155,156-158.

39. Ananth CV, Smulian JC, Vintzileos AM. The effect of placenta previa on neonatal mortality: a population-based study in the United States, 1989 through 1997. *Am J Obstet Gynecol* 2003; May;188(5):1299-304.

40. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta abruption in an Asian population. *Reproductive Sciences* 2007;14(1):59-65.

41. Hung TH, Hsieh CC, Hsu JJ, et al. Risk factors for placenta previa in an Asian population. *Int J Gynecol & Obstet* 2007;97:26-30.

42. Zhu QX, Gao ES, Chen AM, et al. Mifepristone-induced abortion and placenta complications in subsequent pregnancy. *Hum Reprod* 2009;24(2):315-9.

43. Eras JL, Saftlas AF, Triche E, et al. Abortion and its effect on risk of pre-eclampsia and transient hypertension. *Epidemiology* 2000;11:36-43.

44. Trogstad L, Magnus P, Skjaerven R, et al. Previous abortions and risk of pre-eclampsia. *Int J Epidemiology* 2008;37:1333-40.

Supplementary Table A

Comparison of reproductive and perinatal outcomes in the 1st pregnancy (live birth & full term) in women who had induced abortion, livebirth or miscarriage in the 2nd pregnancy

Outcome of 1st pregnancy	Outcome of second pregnancy			Crude Relative Risk (99% CI) [1]	
Live birth	Induced abortion N=30527	Live birth N=125855	Miscarriage N=22404	Induced abortion vs Live birth	Induced abortion vs Miscarriage
Pre-eclampsia	349 (1.1)	1447 (1.2)	325 (1.5)	0.99 (0.85, 1.16)	0.79 (0.65, 0.96)
Placenta previa	128 (0.4)	409 (0.3)	80 (0.4)	1.29 (0.99, 1.67)	1.17 (0.81, 1.69)
Abruptio placenta	84 (0.3)	262 (0.2)	57 (0.3)	1.32 (0.96, 1.82)	1.08 (0.70, 1.68)
Induction of labour[3]	8064 (26.4)	33225 (26.4)	6103 (27.2)	1.00 (0.97, 1.03)	0.97 (0.93, 1.01)
Low birth weight <2500[4]	972 (3.2)	3727 (3.0)	626 (2.8)	1.08 (0.98, 1.18)	1.14 (1.00, 1.30)

Values are n (%) unless otherwise specified

Reproductive outcomes following ectopic pregnancy: a national register based cohort study in Scotland

Supplemental file: STROBE Statement

Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Location within manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title & Abstract: Line 51
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract: Lines 52 - 97
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction: Lines 112 - 159
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction: Lines 161-170
Methods			
Study design	4	Present key elements of study design early in the paper	Methodology: Line 173
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods Lines 178-181
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods: Lines 178 - 207
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods: Lines 213 - 221
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods: Lines 210 - 211.
Bias	9	Describe any efforts to address potential sources of bias	The only possible source of bias could be misclassification of variables as routinely collected data are used. We think that the large dataset should

			compensate for that.
Study size	10	Explain how the study size was arrived at	All available data were included. Power calculation: lines 225 -235.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis: Lines 238-267
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical analysis: Lines 238-267
		(*b*) Describe any methods used to examine subgroups and interactions	Methods: Lines 203 - 207
		(*c*) Explain how missing data were addressed	Methodology: Lines 152 - 159
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable.
		(*e*) Describe any sensitivity analyses	Methodology Lines 261-267
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results: Lines 176 - 177
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	The whole population was selected
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1 and 3
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1 and 3
		(c) Summarise follow-up time (eg, average and total amount)	Table 1 and 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2,4,5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 4, 5
		(*b*) Report category boundaries when	Methods, Tables 2, 4, 5

		continuous variables were categorized	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results: Lines 266-7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion: Lines 341-353
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion: Lines 377-389
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion: Lines 439-449
Generalis-ability	21	Discuss the generalisability (external validity) of the study results	Discussion: Lines 363-373

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Lines 479-480