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SITU KC

Termination of Pregnancy and Its Consequences on Subsequent Birth Outcomes

A nationwide register-based study in Finland

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Tampere University, Faculty of Social Sciences
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Responsible supervisor and Custos
Professor
Suvi Virtanen
Tampere University
Finland

Supervisor
Adjunct Professor
Reija Klemetti
University of Helsinki
Finland

Pre-examiners
Professor Emeritus
Finn Egil Skjeldestad
UiT The Arctic University of Norway
Norway

Professor
Kristina Gemzell Danielson
Karolinska Institutet
Sweden

Opponent
Professor
Oskari Heikinheimo
University of Helsinki
Finland

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ABSTRACT

Termination of pregnancy (TOP) is one of the most common gynaecological procedures performed among women. Around 7600 TOPs were performed in Finland in 2021. In recent decades, medical methods have almost replaced the traditional surgical methods in performing TOPs. Women undergoing TOP are mostly in the onset of their reproductive life and they are likely to become pregnant in later life. There has been a growing concern that TOP might lead to adverse birth outcomes in subsequent birth as regards the method and gestational age at TOP. However, existing studies on adverse birth outcomes after previous TOP and risk factors influencing repeat TOPs have been limited and results are partly inconsistent.

The aim of this study was to investigate the effects of prior TOP on subsequent birth outcomes such as preterm birth, low birth weight, perinatal death and small for gestational age (SGA) according to the TOP method, number of TOPs and gestational age at TOP. The study also assessed the factors influencing the risk of repeat TOPs.

This study includes four sub-studies, which are nationwide register-based studies. Sub-studies I, II and III include all first-time mothers with singleton birth (n=419 879) since 1996-2013 using the linked dataset of the Finnish Medical Birth Register and the Finnish Register of Induced Abortions. The sub-study IV includes women having had TOPs during 1987-2015 (n=193 741) and were identified using the Register of Induced Abortions.

Sub-study I showed increased risk of preterm birth and low birth weight among mothers with prior surgical TOP compared to the mothers with prior medical TOP. When compared with women with no prior TOP, a borderline increased risk for SGA birth was noted among mothers with surgical TOP. Sub-study II could not find any difference in risk of adverse birth outcomes except a marginal increased risk for SGA among women having a surgical TOP compared to women with no TOP. Increased risk of extremely preterm birth was found in women with more than one surgical TOP compared to no TOP.

Sub-study III demonstrated that TOP performed in later gestation was significantly associated with extremely preterm birth, very preterm birth, very low birth weight and small for gestational age in the subsequent birth when compared to the outcomes of women with no prior TOP. The sub-study also reflected higher risks of adverse birth outcomes in the subsequent birth after late-performed TOP than after early performed TOP.

The sub-study IV found out that older age, semi-urban or rural residency, being married or cohabiting and using reliable contraception were protective factors for repeat TOPs, whereas being parous was a risk for repeat TOPs.

In summary, this study indicates that surgical procedure in previous TOP and late-performed TOP are linked with adverse birth outcomes in subsequent birth. Being older, married or cohabiting status and using reliable method of contraception are protective factors for repeat TOPs, whereas being parous is a risk for repeat TOPs. Proper counselling should be provided to women seeking TOP including information on the possible health effects of TOP on subsequent births and the consequences of repeat TOPs. Similarly, initiation of reliable contraception particularly LARC, should be encouraged at the time of TOP to women having had TOP to reduce the number of repeat TOPs.

Keywords: Termination of pregnancy, medical TOP, surgical TOP, repeat TOP, premature birth, low birth weight, perinatal death, small for gestational age, contraception

TIIVISTELMÄ

Raskaudenkeskeytys on yksi yleisimmistä naisille tehtävistä gynekologisista toimenpiteistä. Suomessa tehtiin vuonna 2021 noin 7600 raskaudenkeskeytystä, joissa lääketieteelliset menetelmät ovat viime vuosikymmeninä lähes korvanneet perinteiset kirurgiset menetelmät. Raskaudenkeskeytyksessä olleet naiset ovat pääosin nuoria, hedelmällisen ikänsä alkuvaiheessa olevia, joten monet heistä ovat todennäköisesti raskaana myöhemmässä elämässä. Raskaudenkeskeytysten on arveltu voivan johtaa syntyvien lasten terveysongelmiin naisen myöhemmässä raskaudessa riippuen raskaudenkeskeytyksen menetelmästä ja ajankohdasta, raskausviikoista. Olemassa olevat tutkimukset vastasyntyneisyysajan terveysongelmista raskaudenkeskeytyksen jälkeisessä raskaudessa ja niistä riskitekijöistä, jotka vaikuttavat toistuviin raskaudenkeskeytyksiin, ovat kuitenkin olleet rajallisia, ja tulokset ovat osin epäjohdonmukaisia.

Tämän tutkimuksen tavoitteena oli selvittää käytetyn raskaudenkeskeytysmenetelmän yhteyttä myöhempien raskauksien vastasyntyneisyysajan terveysongelmiin, kuten ennenaikaiseen synnytykseen, alhaiseen syntymäpainoon, perinataalikuolleisuuteen ja syntyneen lapsen raskausviikkoihin nähden pieneen kokoon. Näitä selvitettiin raskaudenkeskeytysmenetelmän, raskaudenkeskeytysten lukumäärän ja ajankohdan mukaan. Tutkimuksessa arvioitiin myös toistuviin raskaudenkeskeytyksiin liittyviä riskitekijöitä.

Tämä väitöskirjatutkimus sisältää neljä valtakunnallista rekisteripohjaista osatutkimusta. Osatutkimuksissa I, II ja III ovat mukana kaikki ensisynnyttäjät, joilla oli yksisikiöinen raskaus vuosina 1996–2013 (n=419 879). Synnyttäjät identifioitiin syntyneiden lasten rekisterin ja raskaudenkeskeytysrekisterin avulla. Osatutkimus IV sisältää ne naiset, joilla oli raskaudenkeskeytyksiä vuosina 1987-2015 (n=193 741) ja jotka identifioitiin raskaudenkeskeytysrekisteristä.

Ensimmäisessä osatutkimuksessa havaittiin kohonnut riski ennenaikaiseen synnytykseen ja alhaiseen syntymäpainoon äideillä, joilla oli aikaisempi kirurginen raskaudenkeskeytys verrattuna äiteihin, joilla oli aikaisempi lääkkeellinen raskaudenkeskeytys. Kirurgisen raskaudenkeskeytyksen jälkeisissä raskauksissa todettiin

lisääntynyt riski ennenaikaiseen synnytykseen ja alhaiseen syntymäpainoon verrattuna niiden naisten raskauksiin, joilla ei ollut ollut aikaisempaa raskaudenkeskeytystä.

Toisessa osatutkimuksessa ei havaittu eri keskeytysmenetelmien mukaisia eroa vastasyntyneisyysajan terveysongelmien yleisyydessä, lukuun ottamatta hyvin pientä lisääntynyttä riskiä syntyneen lapsen pienikokoisuuteen niillä naisilla, joilla oli ollut kirurginen raskaudenkeskeytys verrattuna naisiin, joilla ei ollut ollut raskaudenkeskeytystä. Hyvin ennenaikaisen synnytyksen kohonnut riski todettiin naisilla, joilla oli useampi kuin yksi kirurginen raskaudenkeskeytys verrattuna niihin naisiin, joilla ei ollut ollut raskaudenkeskeytystä.

Kolmas osatutkimus osoitti, että myöhemmillä raskausviikoilla tehty raskaudenkeskeytys oli yhteydessä erittäin ennenaikaiseen synnytykseen, ennenaikaiseen synnytykseen, erittäin alhaiseen syntymäpainoon ja raskausviikkoihin nähden pienikokoiseen lapseen myöhemmässä raskaudessa, kun tuloksia verrattiin niiden naisten raskauksiin, joilla ei ollut aikaisempaa raskaudenkeskeytystä. Osatutkimuksessa saatiin myös viitteitä siitä, että myöhemmillä raskausviikoilla tehtyyn raskaudenkeskeytykseen liittyy myöhemmässä raskaudessa suurempia riskejä kuin varhain tehtyyn raskaudenkeskeytykseen.

Neljännen osatutkimuksen mukaan korkeampi ikä, taajamassa tai maaseudulla asuminen, avo- tai avioliitossa eläminen sekä luotettavan ehkäisyn käyttö olivat toistuvilta raskaudenkeskeytyksiltä suojaavia tekijöitä, mutta synnyttäneisyys lisäsi riskiä toistuviin keskeytyksiin.

Yhteenvetona voidaan todeta tämän tutkimuksen osoittavan, että kirurgiset ja myöhemmillä raskausviikoilla tehdyt raskaudenkeskeytykset ovat yhteydessä vastasyntyneisyysajan terveysongelmiin myöhemmässä synnytyksessä. Korkeampi ikä, avo- tai avioliitossa eläminen sekä luotettavan ehkäisyn käyttö ovat toistuvilta raskaudenkeskeytyksiltä suojaavia tekijöitä, mutta synnyttäneisyys lisää riskiä toistuviin keskeytyksiin. Raskaudenkeskeytystä hakeville naisille tulee tarjota asianmukaista neuvontaa sisältäen tietoa raskaudenkeskeytysten mahdollisista terveysvaikutuksista myöhemmissä synnytyksissä ja toistuvan raskaudenkeskeytyksen seurauksista. Myös luotettavan ehkäisyn, erityisesti pitkäaikaisen ehkäisyn aloittamista raskaudenkeskeytyksen jälkeen tulisi suosia vähentämään toistuvia raskaudenkeskeytyksiä.

Avainsanat: Raskaudenkeskeytys, lääkkeellinen raskaudenkeskeytys, kirurginen raskaudenkeskeytys, ennenaikainen synnytys, alhainen syntymäpaino, perinataalikuolleisuus, pienikokoisuus raskausviikkoihin nähden, raskaudenehkäisy

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ABBREVIATIONS

CI	Confidence Interval
D&C	Dilation and Curettage
D&E	Dilation and Evacuation
HR	Hazard Ratio
LARC	Long-Acting Reversible Contraception
OR	Odds Ratio
SGA	Small for gestational age
THL	Finnish Institute for Health and Welfare
TOP	Termination of Pregnancy

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to throughout the text by their Roman numerals:

I. KC, S., Hemminki, E., Gissler, M., Virtanen, S.M., & Klemetti, R. (2017). Perinatal outcomes after induced termination of pregnancy by methods: A nationwide register-based study of first births in Finland 1996-2013. *PLOS ONE*, 12(9), e0184078.

II. KC, S., Gissler, M., Virtanen, S.M., & Klemetti, R. (2017). Risks of Adverse Perinatal Outcomes after Repeat Terminations of Pregnancy by their Methods: a Nationwide Register-based Cohort Study in Finland 1996–2013. *Paediatric and Perinatal Epidemiology,* 31(6), 485-492.

III. KC, S., Gissler, M., & Klemetti, R. (2020). The duration of gestation at previous termination of pregnancy and its impacts on subsequent birth- a nationwide registry-based study. *Acta Obstetricia et Gynecologica Scandinavica,* 99(5), 651-659.

IV. KC, S., Gissler, M., Heino, A., & Klemetti, R. (2023). Factors influencing the risk of repeat termination of pregnancy: A register-based study in Finland. *Sexual and Reproductive Healthcare*, 37, 100876.

1 INTRODUCTION

Termination of pregnancy (TOP) is one of the most common gynaecological procedures and each year, over 73 million TOPs are performed worldwide (Bearak et al., 2020). Even if the rate of TOP is low (6.7 per 1000 women of childbearing age) in Finland, 7600 TOPs were performed in 2021 (THL, 2021). Despite the fact that TOPs among teenage girls have reduced in recent years in Finland, it cannot be ignored that most of the women undergoing TOP are in the beginning of their reproductive age and many of them wish to become pregnant again in later life (Heikinheimo et al., 2009; THL, 2021). It is possible that TOP might lead to adverse outcomes in subsequent birth. Thus, the influence of TOP on future birth outcomes remains a global public health issue.

Several studies have been conducted previously on TOP and its influence on future pregnancy outcomes; however, the results are contradictory. Some studies concluded that a range of birth outcomes including preterm birth, low birth weight, small for gestational age and perinatal death have been associated with pre-birth TOP (Bhattacharya et al., 2012; Klemetti et al., 2012; Lowit et al., 2010; Saccone et al., 2016; Shah et al., 2009). Different methodological considerations have been the major reasons for varying results from different studies, such as selection of appropriate comparison group, controlling for different confounders, and not distinguish between induced and spontaneous TOP. Apart from them, failing to distinguish TOP procedures between medical and surgical, not having information on gestational age and grounds for TOP are more commonly observed limitations in earlier studies.

In 2000, medical method of TOP was introduced in Finland and other European countries. Since then, the surgical method of TOP has been almost replaced by the medical method. Thus, it is very important to choose for the safer procedure for terminating pregnancy as regards future pregnancy. Furthermore, increased gestational age at the time of TOP has been associated with increased immediate complications (Bartlett et al., 2004; Mentula et al., 2011). Gestational age at the time

of TOP possibly has long-term effects on future birth outcomes and very little few studies have been done regarding this (Jackson et al., 2007; Kalish et al., 2002).

Moreover, the repeat TOP is another public health concern. Previous literature from well-developed countries including Europe concluded that age, parity, relationship conflict and smoking have been associated with repeat TOPs (Fisher et al., 2005; Heikinheimo et al., 2008; Justrad-Berg et al., 2015; Prager et al., 2007). However, large scale studies on the repeat TOP and its risk factors have been limited and poorly understood.

This study, using the high-quality register-based data from Finland was conducted to investigate the risk of adverse birth outcomes including preterm birth, low birth weight, small for gestational age and perinatal death after prior induced TOP according to the TOP method, number of TOP and gestational age at TOP. Furthermore, the study aimed to explore the effects of sociodemographic factors, factors related to TOP history and contraception on the risk of repeat TOPs using register-based data.

2 LITERATURE REVIEW

2.1 Termination of pregnancy

The term 'termination of pregnancy' describes the deliberate removal of an embryo or foetus from the uterus in order to end a pregnancy. There are different terms used for termination of pregnancy such as abortion, induced abortion, interruption of pregnancy, ending a pregnancy, etc. Nowadays, the term 'termination of pregnancy' is more commonly used in documents and policies, as well as during service provision (Kavanagh et al., 2018; Kaller et al., 2023). The term 'termination of pregnancy' was frequently used in earlier literatures including studies from Finland (Ashok et al., 2004; Mentula et al., 2010; Männistö et al., 2014).

The TOP is an indicator of unintended pregnancies, which address the need for access and availability of family planning services and modern contraceptive methods (Bearak et al., 2018). However, the use of contraceptive methods can somehow reduce the number of unintended pregnancies, but the need for access to safe TOP will never be completely eliminated (Grimes et al., 2006).

2.1.1 Incidence of the termination of pregnancy worldwide

Approximately 73 million TOPs are performed each year throughout the world (Bearak et al., 2020). The annual rate of TOP is 39 per 1000 women of childbearing age (15-44 years) globally in 2015-2019, which is similar compared with the figure in 1990-1994 (40 per 1000 women). The rate of TOP was in a decreasing trend till 2000-2004 after which it began to increase till 2015-2019 (Bearak et al., 2020; Sedgh et al., 2016). The TOP is more likely to occur in low- and middle-income countries than the high-income countries; that is, 44 and 38 per 1000 women in middle- and low-income countries and 15 in high-income countries. The rate of TOP in high-income countries declined by 31% between 1990-1994 and 2015-2019; however, the rate remained similar in low- and middle-income countries between 1990-1994 and

2015-2019 (Bearak et al., 2020; Sedgh et al., 2016). Among the total pregnancies, 48% were unintended, accounting for 121 million unintended pregnancies in 2015-2019 (Bearak et al., 2020). The global unintended pregnancy rate declined from 79 to 64 per 1000 women (15-49 years) from 1990-1994 to 2015-2019; however, the proportion of unintended pregnancies resulting in TOP has increased (Bearak et al., 2020). Of the unintended pregnancies, 61% ended in TOP worldwide (Bearak et al., 2020).

2.1.2 Incidence and trend of termination of pregnancy in Europe and Finland

In Europe, the rate of TOP was 52 per 1000 in 1990-1994 which reduced to 20 per 1000 women of childbearing age during 2015-2019 (Bearak et al., 2020; Sedgh et al., 2016). During 1990-1994, the TOP rate was higher in Eastern Europe (88 per 1000 women of childbearing age) which decreased to 31 per 1000 women of childbearing age during 2015-2019 (Bearak et al., 2020; Sedgh et al., 2016). The rate is lower in Western Europe i.e. 9 per 1000 women of childbearing age. TOP among young women was higher in Northern Europe (17 per 1000 women aged 15-19 years) than other European countries, that is 10-11 per 1000 women aged 15-19 years (Gissler et al., 2011). Marked reduction in TOP among young women was seen in many European countries from 2007 to 2017; however, evidence showed change in age group from 20-24 to 25-29 years in some countries (Fiala et al., 2022).

In the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), the rate of TOP is 12.4 per 1000 women aged 15-49 years (THL, 2019). Among the Nordic countries, the lowest rate of TOP is 7.7 per 1000 women aged 15-49 years in Finland and the highest rate of TOP is 16.4 per 1000 women in Sweden (THL, 2019). TOP among women under 20 is decreasing in all Nordic countries (THL, 2019).

A total of 7600 TOPs were performed in Finland in 2021, with the rate of 6.7 per 1000 women of reproductive age group (15-49 years) (THL, 2021). The number of TOPs has reduced during the last decade. Likewise, the number of TOPs among women under 20 has decreased in recent years (Figure 1). In 2021, there were 5.8 TOPs per 1000 women aged 15-19 years. Most TOPs have been found to be performed in age groups 20-24 accounting for the TOP rate of 10.7 per 1000 women aged 20-24 years; however, the rates have been decreasing in recent years (THL, 2021). More than one in three women who had a TOP in 2021 had undergone a previous TOP. Only 9.3% women having had TOP in 2021 had given birth in the

last two years and 8% had a previous pregnancy resulting in TOP in the last two years.

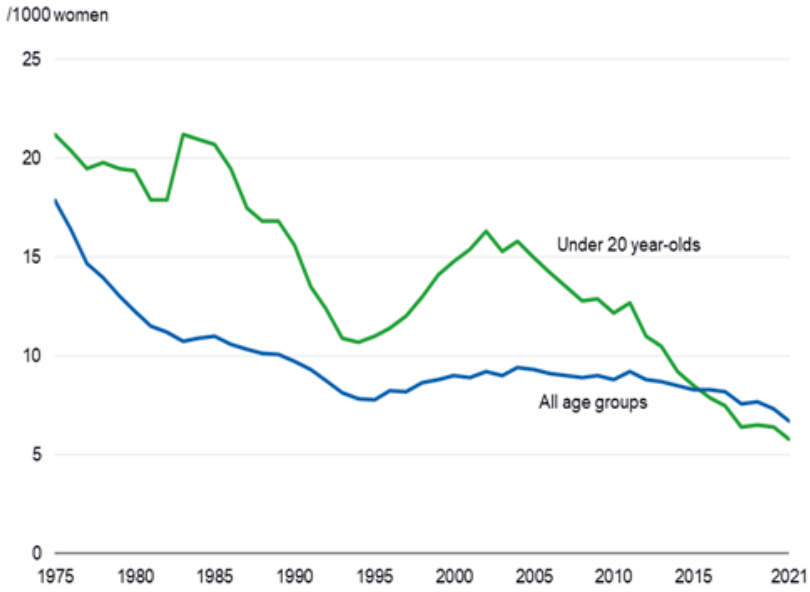

Figure 1. Termination of pregnancy in Finland per 1000 women of same age group 1975-2021 (THL, 2021)

2.1.3 Legislation on termination of pregnancy in Europe and Finland

In most European countries, TOP is allowed on request or on broadened grounds since 2018 (THL, 2021; Fiala et al., 2022). However, restriction on TOP still exists in some countries. Since the 1970s, TOP is easily available and legalized in northern European countries (Gissler et al., 2011). The first country to legalize TOP in Western Europe was the UK in 1967. Following that, a number of countries enacted TOP law in the 1970s (Fiala et al., 2022). The most recent country in Europe to legalize TOP was Republic of Ireland in 2018 and TOP service has been available since January 2019.

In Nordic countries, all women have the right to TOP by law on self-request or with very few restrictions. A woman can request a TOP up to 12 weeks in Nordic countries except, in Sweden up to 18 weeks and in Iceland up to 22 weeks (Fiala et al., 2022; Government of Iceland, 2019). However, in Finland, an approval of one

or two physician is required for TOP up to 12 weeks. In all Nordic countries, TOP can be carried out in later gestational weeks in case of foetal defect and abnormality or to save a woman's life, but an approval from a national authority is required. However, it is suggested that pregnancy should be terminated as soon as possible, preferably before 12 gestational weeks.

Table 1. Legislation on termination of pregnancy in Nordic countries

Country	Year of current legislation	Access to termination of pregnancy on indications and gestational limit	Access to termination of pregnancy in later gestation
Denmark	1973	On request until 12 weeks of gestation	>12 weeks of gestation, with the permission of regional authority
Finland	1970 and 1985	With the permission of one or two physician up to 12 weeks of gestation Due to foetal defect until 24 weeks of gestation	>12 weeks of gestation, with the permission of national authority (Valvira)
Iceland	New legislation came into effect in September 2019	On request up to 22 weeks of gestation	>22 weeks of gestation, with the permission of national authority
Norway	1978	On request up to 12 weeks of gestation	>12 weeks of gestation, with the permission of national authority
Sweden	1975	On request up to 18 weeks On any indication up to viability until 22 weeks	>18 weeks of gestation, with the permission of national authority

Source: Induced abortion in Nordic countries 2019 (THL, 2021)

Before 1950, TOP was illegal in Finland except when continuing the pregnancy posed a risk to a woman's life or health. Since 1950, TOPs were allowed for medical reasons, but the law allowed taking social distress into account (Keski-Petäjä, 2012). In 1970, a more liberal law was introduced which is still in hold today. According to current legislation in Finland, TOP can be allowed up to 20 weeks of gestation or up to 24 weeks in cases of medical condition of a foetus (FINLEX, 1970). Though the legislation is interpreted liberally, an approval from one or two physicians is required up to 12 weeks and an approval from a national authority is required in cases of foetal abnormality and after 12 weeks of gestation. However, the parliament of Finland recently approved reform in TOP law which will be more liberal requiring approval of only one doctor and no reason is required up to 12 gestational week and will be implemented from 1st September 2023 (Sosiaali- ja terveysministeriö, 2022).

A legal TOP can be performed on various grounds such as social, medical and ethical indications. Social indications mean considerable strain caused by living or other conditions (so-called social reasons), including age of woman under 17 or above 40 years, women who have delivered at least four children, and pregnancy and childbirth being a considerable burden to a woman. Medical indications include the pregnancy of a woman being a risk factor for her health or life, mother's and/or father's inability to take care of a child and suspected or confirmed foetal illness or abnormality. Ethical reasons include rape, incest, and other reasons mentioned in the penal law (Knudsen et al., 2003).

Table 2. Legal indications for termination of pregnancy (TOP) by the type of indication in Finland

Type of indication	Indications
Medical	Pregnancy would endanger women's life or health because of illness and physical defect or infirmity
	Confirmed foetal defect such as mental deficiency, severe illness, or handicap
	Maternal or paternal illness and physical anomaly limiting childcare ability
Ethical	Rape, incest, and other reasons mentioned in penal law
Social	Pregnancy and childbirth being unbearable burden to a woman
	Age under 17 years
	Age 40 years or above
	Has delivered four or more children

2.2 Methods of termination of pregnancy

2.2.1 Surgical termination of pregnancy

Surgical methods for TOP were developed and came into practice during the 19th century. Surgical methods are usually performed using dilatation and curettage (D&C or sharp curettage) or vacuum aspiration (also known as vacuum curettage or uterine

aspiration). During dilatation and curettage, the cervix is dilated until a curette (a surgical instrument shaped like a spoon or scoop) can be inserted to remove the contents of the uterus. In some cases, large forceps is used to remove larger parts of the contents. During vacuum aspiration, the cervix is dilated until a cannula of appropriate size can be inserted to remove the uterine contents by suction through vacuum aspiration; it can be manual or electric. Vacuum aspiration is a much safer and less painful and widely used method for terminating the first trimester pregnancy in most countries (Kapp & Lohr, 2020; Wen et al., 2008). For the second trimester TOP, dilation and evacuation (D&E) is usually used from 14 to approximately 24-26 gestational weeks (Kapp & Lohr, 2020). During D&E, the cervix is dilated, and surgical evacuation of the uterus is performed using vacuum or forceps. In all surgical procedures, local or general anaesthesia is required. According to recent WHO guidelines, surgical TOPs should be done using vacuum aspiration before 14 gestation weeks and D&E should be used on or after 14 gestational weeks (WHO, 2022).

Earlier, the common method used for surgical TOP was dilatation and curettage, (Kulier et al., 2001). These days, dilatation and curettage is no longer recommended (WHO, 2022). Nowadays, vacuum aspiration is the most common surgical method in the first trimester TOP (Kulier et al., 2001). Electric vacuum aspiration has been used in China since 1958. Since then, the use of this method has spread to eastern and western Europe, and then to USA for performing surgical TOP prior to 7 weeks (Lichtenberg & Paul, 2013). Both manual and electric vacuum aspiration is found safe and effective for early TOP (Lichtenberg & Paul, 2013; Wen et al., 2008). Cervical preparation using osmotic dilators or pharmacologic agents such as misoprostol, mifepristone or combinations of these before surgical TOP will reduce cervical injury and uterine perforations (Lerma & Blumenthal, 2020; Shaw & Lerma, 2016). The risk is most evident in young, nulliparous women and women with higher gestational weeks (Kulier et al., 2001). Lack of cervical preparation results in increased risk for adverse events in vacuum aspiration and is therefore recommended prior to vacuum aspiration (Meirik et al., 2012; WHO, 2022).

Surgical methods have been practised in terminating pregnancy during both the first and second trimester of pregnancy. Early surgical TOP is safe and effective performed before 7 weeks of gestation (Paul et al., 2002; Upadhyay et al., 2015). Previous studies also reported the high efficacy of vacuum aspiration, with complete TOP rates between 95 and 100% (Lichtenberg & Paul, 2013; Wen et al., 2008; Zhou

et al., 2002). Surgical TOP using dilation and evacuation is also found safe during the second trimester TOP (Autry et al., 2002). Complications such as uterine cervical injuries, excessive blood loss, prolonged bleeding, incomplete removal of foetus or placenta are rare in surgical TOP (Kulier et al., 2001).

2.2.2 Medical termination of pregnancy

Medical TOP is the method of terminating pregnancy using different drugs alone or in combination. Sometimes, terms such as non-surgical or medication TOP are also used to refer to medical termination (WHO, 2018). Various drugs have been used for the first trimester medical TOP. The most widely studied drugs are prostaglandin alone, mifepristone alone, methotrexate alone, mifepristone with prostaglandin, and methotrexate with prostaglandins (Kulier et al., 2011; Zhang et al., 2022).

Before the introduction of modern medical abortion, methods used for abortion were intra- or extra-amniotic prostaglandin analogues, which are no longer recommended (Bygdeman & Gemzell-Danielsson., 2008). Since 1970, medical methods using prostaglandins have been in use. Prostaglandin softens the cervix and enhances uterine contraction, thus helps in expelling the products of conception. Prostaglandins were first used as single agent in terminating pregnancy. Later, combined regimens were used and found more effective than single agent regimen (Kulier et al., 2011; Zhang et al., 2022). The combined regimen of mifepristone followed by suitable prostaglandin analogue (usually misoprostol) has been generally used to terminate a pregnancy. Mifepristone is an antiprogestin, which binds to progesterone receptors inhibiting the action of progesterone and hence interfering the continuation of a pregnancy. Misoprostol is a prostaglandin E1 analogue that can be used either in combination with mifepristone or alone. Nowadays, misoprostol is the choice of prostaglandin and is effective, less costly, stable at room temperature and offers different administration routes (Tang et al., 2002; Zhang et al., 2022).

Medical TOP was first introduced in France and China in 1988. After that, it took a while for it to be extended to several countries. Medical TOP came into use in 1991 in the United Kingdom, 1992 in Sweden and, since 2000, it has been used in most European countries and in the USA. In Finland, the medical method was first used officially in 2000 for TOP with gestational age up to 63 days by means of

administration of mifepristone followed by misoprostol. Nowadays, almost 98% of TOPs are performed using medical methods in Finland (THL, 2021).

Since the beginning of medical termination using mifepristone and misoprostol, different doses of medications have been used. According to the WHO recommendation, the combination used for termination of first trimester medical TOP is 200 mg oral mifepristone, followed 24-48 hours later by 800μg of misoprostol by buccal, sublingual or vaginal administration (Ireland et al., 2015; Kulier et al., 2011; WHO, 2018; WHO 2022). Similarly, the recommended doses for second trimester TOP is 200 mg of oral mifepristone followed after 24-48 hours by 400μg of misoprostol administered vaginally, sublingually or buccally every 3 hours until expulsion (Gemzell-Danielsson & Lalitkumar, 2008; WHO, 2018; WHO, 2022). It is also suggested to use a combined regimen of letrozole and misoprostol for first trimester TOP (WHO, 2022). The recommended dose is 10mg letrozole orally each day for 3 days followed by 800μg of misoprostol sublingually on the fourth day (WHO, 2022).

Different routes for misoprostol administration such as oral (immediately swallowing pills), buccal (holding pills in the cheek) and sublingual (holding pills under the tongue) have been studied as an alternative method to vaginal administration for medical TOP. The vaginal route of misoprostol administration is more effective than oral administration and has fewer side effects than the oral, sublingual and buccal route (Ho et al., 1997; Kulier et al., 2001; Raymond et al., 2013; Winikoff et al., 2008; Zhang et al., 2022). The side effects of medical TOP in the first trimester are usually mild including nausea, vomiting, fever, diarrhoea and abdominal pain and adverse effects are rare (Kapp et al., 2019; Kulier et al., 2001; Lohr et al., 2008; Zhang et al., 2022). These side effects may vary according to the regimen used for medical termination and gestational age at termination (Say et al., 2005; Spitz et al., 1998).

Previously, medical methods were used to terminate pregnancy usually in early pregnancy. Later, the methods were approved for second trimester termination as well. Medical TOP has been more common in Nordic countries since the combined regimen of mifepristone and prostaglandin was introduced (Gemzell-Danielsson & Lalitkumar, 2008).

The efficacy of medical TOP is usually defined as the termination with complete expulsion of the conceptus without requiring surgical procedure (Spitz et al., 1998).

The efficacy of medical methods of TOP have been found high in both first and second trimester TOP. Medical methods of TOP using mifepristone and misoprostol is found effective and acceptable (Kapp et al., 2019; Kulier et al., 2001; Lohr et al., 2008; Raymond et al., 2013; Zhang et al., 2022). However, gestational age affects the efficacy of medical TOP regimen with decreasing efficacy after 9 weeks of gestation (Ireland et al., 2015; Winikoff et al., 2008). In a review where medical TOP is compared with surgical TOP, the efficacy rate of late first trimester medical TOP was 94.6% (Kapp et al., 2019). Serious complications such as uterine rupture, major haemorrhage, need for blood transfusion, cervical tear are rare (Gemzell-Danielsson & Lalitkumar, 2008; Lohr et al., 2008). A large study reported that the success rate of TOP at 13-21 weeks is more than 97% with only 8% requiring surgical intervention (Ashok et al., 2004). A Finnish register-based study comparing the complications after first and second trimester TOP, found that second trimester TOP was associated with increased risk of surgical evacuation and infection (Mentula et al., 2011).

2.2.3 Change in method of termination of pregnancy (TOP)

Over the past three decades, medical TOP has been developed and increasingly used throughout the world (Table 3). In Finland, medical TOP officially began in 2000 with gestational age up to 63 days. Medical methods have almost completely taken the place of surgical termination methods and almost 98% of all terminations were performed using medical methods in 2021 (Figure 2). The increasing trend of medical TOP is similar before 12 gestational weeks and 9 gestational weeks (Figure 3 and 4). Before 2000, prostaglandins were used for terminating a pregnancy (Figure 2). The increasing use of medical TOP is observed in other Nordic countries; around 94% of TOPs are performed medically in Sweden and Norway (THL, 2021). Although the use of medical TOPs is lower in England and Wales (85%) and the United States (54%), the trend is increasing each year (Department of Health, 2021; Guttmacher Institute, 2021). Similarly, the use of medical TOP is increasing in all European countries, although there was less use of medical TOP in Germany, Netherland and Italy (Miani, 2021).

Table 3. Use of medical termination of pregnancy (TOP) in Europe and United States (percentage of all TOPs)

Country	Termination of pregnancy (%)	Year	Source
Finland	98%	2021	THL, 2021
Denmark	75%	2018	THL, 2021
Iceland	79%	2018	THL, 2021
Norway	94%	2020	NIPH, 2020
Sweden	96%	2021	National Board for Health and Welfare, 2021
United States	54%	2020	Guttmacher Institute 2022
England and Wales	85%	2020	Department of Health and Social Care 2021
France	70%	2019	Miani, 2021
Germany	28%	2019	Miani, 2021
Scotland	88%	2019	Miani, 2021
Netherland	26%	2018	Miani, 2021
Switzerland	74%	2019	Miani, 2021
Italy	24%	2018	Miani, 2021
Slovenia	72%	2019	Miani, 2021
Portugal	68 %	2018	Miani, 2021

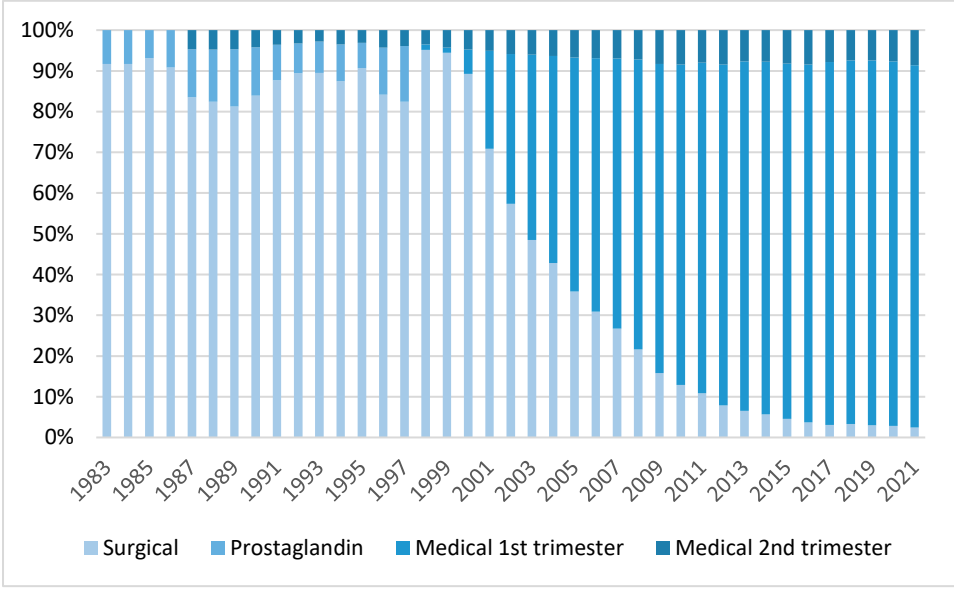

Figure 2. Methods of termination of pregnancy (TOP) for all gestational age in Finland 1983-2021 (THL, 2021)

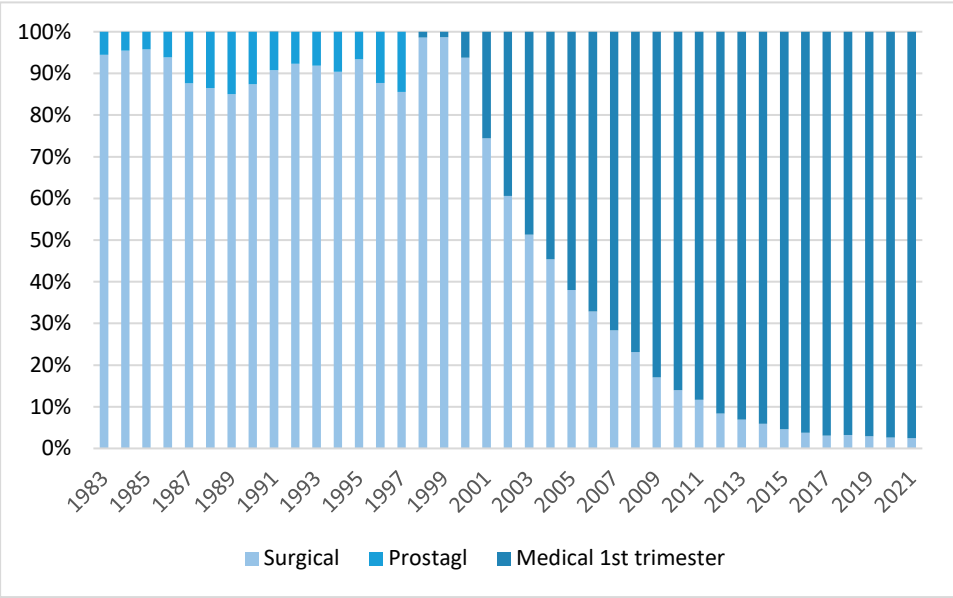

Figure 3. Methods of termination of pregnancy (TOP) for less than 12 gestation weeks in Finland 1983-2021 (THL, 2021)

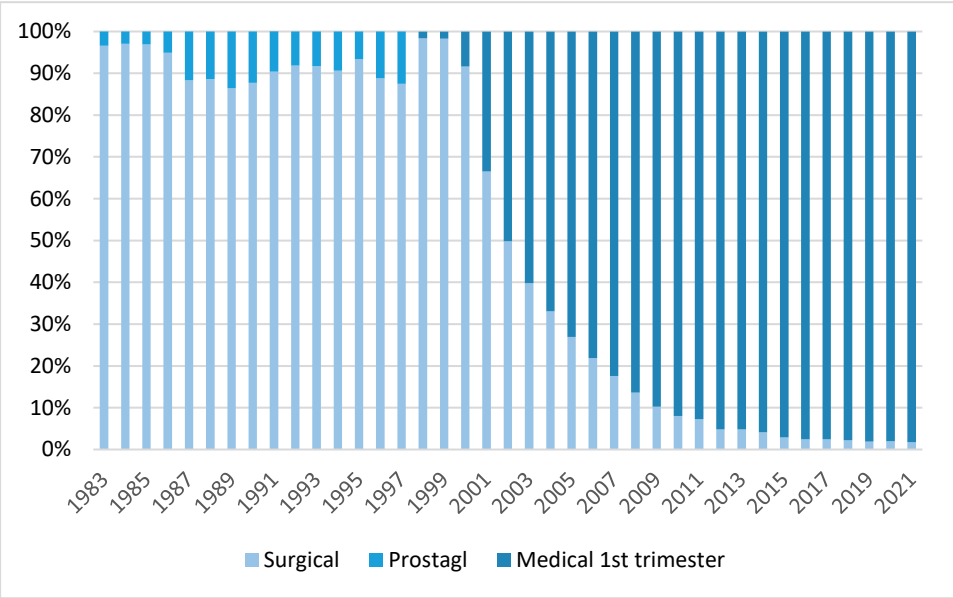

Figure 4. Figure 4: Methods of termination of pregnancy (TOP) for less than 9 gestation weeks in Finland 1983-2021 (THL, 2021)

2.3 Effects of termination of pregnancy (TOP) on subsequent birth outcomes

The long-term effect of TOP on subsequent births has been less studied. Several adverse events such as increased risk for preterm birth, low birth weight, small for gestational age, and perinatal death have been associated with TOP. The biological mechanism regarding previous termination of pregnancy and subsequent birth outcomes such as preterm birth, low birth weight, small for gestational age and perinatal death is completely not clear. During a normal birth, dilatation of the cervix occurs gradually over a period of many hours, while during the induced TOP, particularly the surgical TOP, mechanical dilatation of the cervix is required (Kulier et al., 2001). The mechanical or rapid dilatation during the surgical TOP procedure may cause physical injury to the cervix which may affect future birth outcomes. There are a few suspected mechanisms which could explain the possible role of induced TOP on adverse birth outcomes, especially preterm birth. Infection before or after the surgical procedures may be one reason for preterm birth in subsequent pregnancy (Ancel et al., 2004; Henriet & Kaminski, 2001). Women with prior TOP have an increased risk of intra-amniotic infection. Surgical TOP also causes mechanical trauma to the cervix leading to the increased risk of cervical insufficiency (Ancel et al., 2004; Watson et al., 2012). It has been also suggested that cervical damage might impair the antimicrobial defence mechanism due to cervical trauma which results in ascending infection (Lemmers et al., 2016; Svare et al., 1992). Furthermore, surgical TOP may cause abnormal placentation damaging the endometrial lining, that may increase the risk of preterm birth (Ancel et al., 2004). Previous TOP has been linked to placenta previa, pre-eclampsia and intra-uterine growth restriction, which could lead to adverse birth outcomes (Watson et al., 2012; Zhou et al., 2000). Perinatal outcomes are interlinked, and it is likely that the phenomenon and its explanation is the same for SGA and perinatal death as for preterm birth.

2.3.1 Preterm birth

According to the World Health Organization (WHO), preterm birth is defined as being born before 37 weeks of pregnancy (WHO, 2011). Based on gestational age, preterm birth can be further divided into three sub-categories; extremely preterm birth (less than 28 weeks of gestation), very preterm birth (birth from 28 weeks to less than 32 weeks of gestation) and moderate to late preterm birth (birth from 32 weeks to less than 37 weeks) (WHO, 2011).

Preterm birth is one of the leading causes of morbidity and mortality among children under 5 years and it is the most important cause of neonatal mortality (Liu et al., 2015; UN IGME, 2021). Late preterm birth covers the largest proportion of the singleton preterm births and the risk of mortality and morbidity is lower in late preterm than the early preterm births (Saigal & Doyle, 2008; Teune et al., 2011). However, the risk is higher in late preterm than the term births (Teune et al., 2011). Babies who are born prematurely face higher risks of serious health problems and disabilities such as cerebral palsy, intellectual impairment, chronic lung disease, metabolic disorders, and vision and hearing loss (Mwaniki et al., 2012; Platt, 2014; Saigal & Doyle, 2008; WHO, 2012). Premature birth before 37 weeks of gestation is 4.9% in Finland (THL, 2020). There is no much change in preterm delivery in Finland over the study period (1996-2020) (Figure 5).

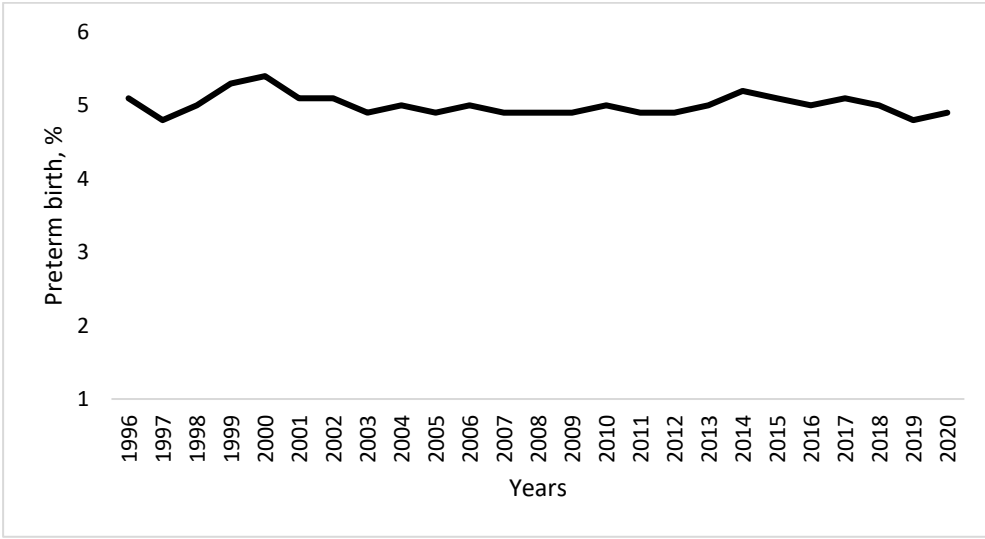

Figure 5. Preterm births in Finland during the years 1996-2020 (THL, 2020)

Preterm birth concerning TOP has been the most studied outcome and there are only a few studies on other birth outcomes (Van Oppenraaij et al., 2009). Early studies reported that surgical TOP in the first trimester does not increase the risk of premature delivery (Atrash & Hogue, 1990; Frank et al., 1991); however, the earlier studies were mostly based on surgical TOP. Results regarding the association between TOP and preterm birth from earlier and recent studies are still conflicting. According to some recent studies (Saccone et al., 2016; Shah et al., 2009), there is association between preterm birth and prior TOP. In a review study by Thorp et al., that included 24 studies, of which 12 studies reported on preterm birth and TOP, the risk ratio for preterm birth ranged from 1.3-2.0 (Thorp et al., 2003). A dose-response relationship was observed in seven studies out of 12 (Thorp et al., 2003). Similarly, in a systematic review including 22 studies, a clear association was found between preterm birth and TOP with a dose-response relationship (Shah et al., 2009). Women with a history of a single TOP was significantly associated with preterm birth (OR 1.27, 95% CI 1.12-1.44) compared with women with no such history (Shah et al., 2009). The risk of preterm birth increased with the increasing number of TOPs; a history of more than one TOP is associated with increased risk (OR 1.62, 95% CI 1.27-2.07) (Shah et al., 2009). A similar result was found in another meta-analysis including 12 studies (Swingle et al., 2009). A history of a single TOP was associated with increased risk for preterm birth (OR 1.25, 95% CI 1.03-1.48) and the risk was even higher as the number of TOPs increased (OR 1.51, 95% CI 1.21-1.75) (Swingle et al., 2009). The study also reported increased risk for very preterm birth below 32 weeks of gestation after TOP (OR 1.64, 95% CI 1.38-1.91). Similarly, in a recent meta-analysis including 31 studies, higher risk of preterm birth was found among the women with surgical TOP compared to women without a history of termination (OR 1.25, 95% CI 1.13-1.38) (Saccone et al., 2016). Sub-analysis showed that women with only one prior surgical TOP had a higher risk of preterm birth (OR 1.53, 95% CI 1.02-2.31) compared to those who did not have any history of TOP. The risk got even higher among women with more than one TOP compared with those having no such history of termination (OR 1.98 95% CI 1.46-2.68). In sub-analysis, increased risk after TOP was noted in case control studies while similar risk was seen among women having had a history of TOP and those with no history of TOP in cohort studies. When analysis was limited to the first trimester TOP before 14 weeks, there was no difference in risk of preterm birth. Regarding medical TOP, only three studies included medical TOP in this meta-

analysis and there was no difference in risk of preterm birth (Saccone et al., 2016). A meta-analysis and systematic review by Lemmers et al., including 21 studies, reported that women with history of dilatation and curettage compared with no such history had increased risk for preterm birth <37 weeks (OR 1.29, 95% CI 1.17-1.42), very preterm birth <32 weeks (OR 1.69, 95% CI 1.20-2.38), and extremely preterm birth (OR 1.68, 95% CI 1.47-1.92) (Lemmers et al., 2016). The risk for preterm birth was higher after dilatation and curettage compared to women with medically managed TOP or miscarriage (OR 1.19, 95% CI 1.10-1.28).

Large-scale population-based studies have been published exploring the association between preterm birth and TOP. A large Finnish study using Finnish register data found no significant increased risk of preterm birth and very preterm birth after one TOP. However, an increased risk was found for very preterm birth (less than 28 weeks of gestation) after more than one TOP when comparing mothers with no previous TOP and mothers with previous TOP (Klemetti et al., 2012). Dose-response effect was seen in the study; the risk increased as the number of prior TOP increased. The risk for very preterm birth was higher after two prior TOPs compared with those mothers without a history of TOP (OR 1.71, 95% CI 1.15-2.54) and the risk was even higher among mothers with three or more prior TOPs (OR 2.81, 95% CI 1.49-5.29) (Klemetti et al., 2012).

A large cohort study using the Scotland national register explored the reproductive outcomes in women following TOP (Bhattacharya et al., 2012). The study found an increased risk of preterm birth in women having had TOP in the first pregnancy compared with primigravid women (adjusted RR 1.37, 95% CI 1.32-1.42) (Bhattacharya et al., 2012). However, the dose-response effect was not seen in this study. The study also explored the risk of preterm birth in women having had surgical and medical TOP. Surgical TOP was associated with increased risk of spontaneous preterm birth in comparison with medical TOP (Bhattacharya et al., 2012). Similar results were observed in a prospective cohort study that showed the increased risk of preterm birth after a single TOP managed by cervical dilatation and curettage (OR 1.48, 95% CI 1.04-2.10) (McCarthy et al., 2013). Due to the small data size, dose-response effect could not be assessed in the study (McCarthy et al., 2013). Likewise, a study from China showed the increased risk of preterm birth after repeated medical TOPs compared with repeated surgical TOPs, OR 1.22, 95% CI 1.03-1.64 (Liao et al., 2011). However, the study found no association between preterm delivery in the first subsequent pregnancy among the women with a history

of multiple medical TOP compared with those with no such history (Liao et al., 2011).

Another large population-based study was conducted in Scotland in 2013 that suggested no association between TOP and increased risk for preterm delivery (Woolner et al., 2014). This was in contrast with the findings of previous studies (Bhattacharya et al., 2012; Liao et al., 2011; McCarthy et al., 2013). Similarly, a Danish study found no significant increased risk of preterm birth and medical TOP (Virk et al., 2007). Another study from China also suggested no adverse birth outcomes after a single medical TOP compared with no TOP (Chen et al., 2004). The study found the lower preterm delivery (OR 0.77, 95% CI 0.61-0.98) after one mifepristone-induced TOP but no difference in outcome among women with medical TOP compared with women with surgical TOP (Chen et al., 2004).

Very few studies have taken into account the gestational age at TOP regarding the risk of preterm birth after TOP, and little is known concerning second trimester TOP (Jackson et al., 2007; Kalish et al., 2002). Most of those studies have been focused on surgical methods and revealed that dilation and evacuation in the second trimester does not increase the risk of preterm birth (Jackson et al., 2007; Kalish et al., 2002; Schneider et al., 1996a). Only a few studies focused on medical TOPs (Männistö et al., 2014; Mirmilstein et al., 2009). A Finnish study assessing short-term complications suggested a higher risk of surgical evacuation and infection after second trimester medical TOP compared with first trimester medical TOP (Mentula et al., 2011). One small Australian study concerned the risk of preterm birth after medical TOP using misoprostol and mifepristone and revealed the risk of preterm birth was not increased after second trimester medical TOP compared with the risk after no history of TOP (Mirmilstein et al., 2009). However, the background information was incomplete, and the confounders were not taken into account. Similarly, a study from Finland also supported this finding suggesting second trimester TOP performed on primigravid women was not associated with risk of preterm birth (Männistö et al., 2014).

The procedure of TOP has been changing dramatically and this rapid change should be considered while studying the association between the TOP and risk of subsequent birth outcomes. A study conducted in Scotland explored how the association between TOP and preterm birth changed during 1980–2000 (Oliver-Williams et al., 2013). When analysed by the year of delivery, the strongest association

was observed in 1980–1983 (OR 1.32, 95% CI 1.21-1.43), the association declined between 1984 and 1999 and no significant association was found after 2000. The authors suggested that the reason for this decreasing association was the change in the method, i.e increasing use of medical methods and the use of cervical pre-treatment prior to perform the surgical method in order to reduce damage to the cervix.

Table 4. Studies on the risk of preterm birth after termination of pregnancy (TOP) on subsequent births

Study	Design	Country, Study period	Study population (Number, n)	Comparison	Risk of preterm birth	Dose response effect
Ke et al., 2018	Retrospective cohort study	2015 Jan-Dec, Southern China	First time mothers with singleton birth (n=3684)	Prior TOP vs no TOP	OR 0.80 (95% CI 0.53-1.20)	NA
Saccone et al., 2016	Meta-analysis	1982-2014	Number of studies=16	At least one surgical TOP vs no history of TOP	OR 1.25 (95% CI 1.13-1.38)	Yes
Männistö et al., 2014	Register-based study	2000-2009	Primigravid women who underwent medical TOP and had subsequent pregnancy ending in live birth (n=3843)	Second trimester medical TOP vs first trimester medical TOP	OR 0.97 (95% CI 0.68-2.01)	NA
Männistö et al, 2013	2000-2009	Register-based study	Primigravid women who underwent medical and surgical TOP during first trimester of pregnancy and whose subsequent pregnancy resulted in singleton delivery (n=8294)	Medical vs surgical TOP	OR 0.87 (95% CI 0.68-1.13)	NA

McCarthy et al, 2013	Prospective cohort study	2004-2011	Nulliparous women with a singleton pregnancy (n=5575)	One TOP vs no previous pregnancy loss	OR 1.48 (95% CI 1.04-2.10)	No
Woolner et al., 2013	Register based study	1986-2010, Scotland	Women who had TOP in first pregnancy (n=45632)	Previous TOP vs primigravid women Medical TOP vs Surgical TOP	OR 1.05 (95% CI 0.88-1.32) OR 0.97 (95% CI 0.62-1.53)	NA
Klemetti et al., 2012	Population-based study	1996-2008, Finland	First time mothers with singleton birth (n=300858)	Two TOP vs no history of TOP	OR 1.71 (95% CI 1.15-2.54) (Very preterm birth)	Yes
Bhattacharya et al., 2012	Retrospective cohort study	1981-2007, Scotland	Women who had TOP, miscarriage or live or an ongoing pregnancy and live delivery following a second pregnancy (n=624865)	TOP vs primigravid women Surgical TOP vs medical TOP	RR 1.37 (95% CI 1.32-1.42) RR 1.25 95% CI (1.07-1.45)	No
Liao et al., 2011	Prospective cohort study	2006-2009	Pregnant women with one or more medical or surgical TOP or no history of TOP (n=18024)	Multiple Surgical TOP vs Multiple Medical TOP	OR 1.22 (95% CI 1.03-1.64)	No

Shah et al., 2009	Meta-analysis	1982-2006	Number of studies=13	One TOP vs no history of TOP	OR 1.27 (95% CI 1.12-1.44)	Yes
Swingle et al., 2009	Meta-analysis	1988-2006	Number of studies=12	One surgical TOP vs no history of TOP	OR 1.25 (95% CI 1.03-1.48)	Yes
Virk et al., 2007	Register based cohort study	1999-2004, Denmark	Women who had gone through TOP for non-medical reasons and pregnant later (n=11682)	Medical TOP vs surgical TOP	RR 0.88 (95% CI 0.66-1.18)	NA
Chen et al., 2004	Prospective cohort study	1998-2001	Pregnant women having history of first trimester TOP (either medical or surgical) or no TOP (n=14656)	Medical TOP vs no history of TOP Medical TOP vs surgical TOP	OR 0.77 (95% CI 0.61-0.98) OR 0.94 (95% CI 0.74-1.20)	No

2.3.2 Low birth weight

Birth weight is the first weight of an infant recorded after birth (WHO, 2011). Birth weight is categorized as low birth weight, very low birth weight and extremely low birth weight. According to the World Health Organization (WHO), low birth weight is defined as weight at birth less than 2500g, very low birth weight is weight at birth less than 1500g and extremely low birth weight is weight at birth less than 1000g (WHO, 2011). Low birth weight is also a major public health issue with long-term consequences such as increased morbidity and mortality in infancy as well as in later life and was associated with cardiovascular diseases, respiratory disorders, stroke and diabetes type II (Class et al., 2014; Watkins et al., 2016).

Several studies have been done concerning the association between previous TOP and low birth weight. Early studies focusing on surgical TOP found no significantly increased risk for low birth weight following vacuum aspiration (Atrash & Hogue, 1990; Frank et al., 1991). A study done in Scotland suggested that TOP in the first pregnancy did not significantly increase the risk of low birth weight in primigravid women (Woolner et al., 2014). Similarly, a recent Chinese study also reported lack of association between low birth weight and previous TOP (Ke et al., 2018).

A meta-analysis was performed including 18 studies regarding the association between TOP and low birth weight and revealed a significantly increased adjusted risk of low birth weight (OR 1.47, 95% CI 1.24-1.73) after more than one TOP compared with women with no such history of TOP (Shah et al., 2009). Similar findings were observed in a large Finnish population-based study, that found a significant increased risk of low birth weight (OR 1.43, 95% CI 1.12-1.84) and very low birth weight (OR 2.25, 95% CI 1.43-3.52) only among women with a history of three or more TOPs (Klemetti et al., 2012). Similarly, higher risk of low birth weight was found among adolescents with a previous TOP (OR 2.74, 95% CI 1.06-7.09) compared with nulliparous adolescents (Reime et al., 2008). A Danish cohort study also suggested a positive association between one (OR 1.9, 95% CI 1.6-2.3) and two or more TOPs (OR 1.9, 95% CI 1.3-2.7) and low birth weight (Zhou et al., 2000).

Only a few studies concerned the method of TOP while studying the association between previous TOP and low birth weight. In a Danish cohort study, medical

TOP in the first trimester did not increase the risk of low birth weight compared with surgical TOP (Virk et al., 2007). There was no increased risk of low birth weight among women having had a medical TOP compared with the women having had surgical TOP or no TOP (Chen et al., 2004; Yimin et al., 2004). A study from Finland comparing the birth outcomes after first and second trimester medical TOPs (Männistö et al., 2014) found no increased risk of low birth weight after the second trimester TOP compared with the first trimester TOP (OR 1.47, 95% CI 1.24-1.73).

Table 5. Studies on risk of low birth weight after termination of pregnancy (TOP) on subsequent births

Study	Design	Country, Study period	Study population	Comparison	Risk of low birth weight
Ke et al., 2018	Retrospective cohort study	2015 Jan-Dec, Southern China	First time mothers with singleton birth (n=3684)	Prior TOP vs no TOP	OR 0.86 (95% CI 0.57-1.31)
Männistö et al., 2014	Register based study	2000-2009, Finland	Primigravid women who underwent medical TOP and had subsequent pregnancy ending in live birth (n=3843)	Second trimester TOP vs first trimester TOP	OR 1.16 (95% CI 0.68-2.01)
Männistö et al, 2013	Register-based study	2000-2009, Finland	Primigravid women who underwent medical and surgical TOP during first trimester of pregnancy and whose subsequent pregnancy resulted in singleton delivery (n=4853)	Medical vs surgical TOP	OR 0.90 (95% CI 0.68-1.19)
Woolner et al., 2013	Register based study	1986-2010, Scotland	Women who had TOP in first pregnancy (n=45632)	Previous TOP vs primigravid women Medical TOP vs Surgical TOP	OR 1.14 (95% CI 0.94-1.39) OR 1.02 (95% CI 0.78-1.32)
Klemetti et al., 2012	Population-based study	1996-2008, Finland	First time mothers with singleton birth (n=300858)	Three or more TOP vs no history of TOP	OR 1.43 (95% CI 1.12-1.84)
Shah et al., 2009	Meta-analysis	1982-2006	Number of studies=5	At least one TOP vs no history of TOP	OR 1.47 (95% CI 1.24-1.73)

Virk et al., 2007	Register-based cohort study	1999-2004, Denmark	Women who had gone through TOP for non-medical reasons and pregnant later (n=11682)	Medical TOP vs surgical TOP	RR 0.82 (95% CI 0.61-1.11)
Chen et al., 2004	Prospective cohort study	1998-2001, China	Pregnant women having history of first trimester TOP (either medical or surgical) or no TOP (n=4925)	Medical TOP vs no history of TOP Medical TOP vs surgical TOP	OR 0.96 (95% CI 0.71-0.29) OR 1.16 (95% CI 0.85-1.58)

2.3.3 Small for gestational age

According to the International Societies of Pediatric Endocrinology and The Growth Hormone Research Society, small for gestational age (SGA) was defined as birth weight more than 2 SDs below the sex- and gestational age-specific reference mean (Clayton et al., 2007).

Many studies have been conducted to study the effect of TOP on low birth weight. However, very little is known regarding whether there is an association between TOP and small for gestational age birth. A meta-analysis including three studies concerning the effect of TOP on the risk of SGA by Shah et al., 2009 reported no association between TOP and SGA. Similar results showing no risk of SGA after TOP were reported by other studies (Henriet & Kaminski, 2001; McCarthy et al., 2013; Parazzini et al., 2007; Raatikainen et al., 2006). However, these studies did not consider the method of TOP or gestational age at the time of TOP. A population-based study from Finland reported that medical TOP was not associated with SGA when compared with surgical TOP (Männistö et al., 2013). Another study by Männistö et al. in 2014 on the risk of adverse birth outcomes after TOP by gestational age reported that second trimester TOP was not associated with SGA compared with the first trimester TOP. A recent meta-analysis including three studies reported a slightly higher risk of SGA (OR 1.19, 95% CI 1.01-1.42) after one surgical TOP compared with one medical TOP (Saccone et al., 2016).

2.3.4 Perinatal death

Perinatal death is the death of a foetus weighing at least 500g after 22 completed weeks of gestation and the number of early neonatal deaths up to 7 completed days after birth. The perinatal death rate in Finland is 3.9 per 1000 births (unpublished data THL, 2019). Only a couple of studies considered perinatal death while looking at birth outcomes and TOP. A large register-based study from Finland reported a small increased risk of perinatal death after one pre-birth TOP (OR 1.19 95% CI 1.02-1.39) (Klemetti et al., 2012). In contrast, a review study done by Van Oppenraaij et al. in 2007 reported no association between perinatal death and previous TOP.

2.4 Repeat termination of pregnancy and associated factors

The term 'repeat termination of pregnancy' (repeat TOP later on) refers to more than one TOP ever (Rowlands et al., 2014). Repeat TOP is highly prevalent worldwide and the figure varies between different countries. The proportion of women having repeat TOPs accounts for 50% in the United States, 43% in England and Wales, 46% in Sweden and 36.7% in Norway (Department of Health, 2021; Guttmacher Institute, 2019; Justad-Berg et al., 2015; National Board for Health and Welfare, 2021). In Finland, more than one in three women is likely to experience repeat TOP, i.e. 37% of women having had TOP had gone through at least one previous TOP (THL, 2021).

Several studies from different countries such as Canada, UK, the USA and European countries found that the repeat TOP was linked with age (Fisher et al., 2005; Heikinheimo et al., 2008; Justad-Berg et al., 2015; Mccall et al., 2016; Prager et al., 2007; Stone & Ingham, 2011), parity (Li et al., 2021; Mccall et al., 2016; Stone & Ingham, 2011), use of contraception (Heikinheimo et al., 2008; Mccall et al., 2016; Niinimäki et al., 2009; Stone & Ingham, 2011), and history of prior TOP (Heikinheimo et al., 2008; Heikinheimo et al., 2009). Other factors such as smoking, alcohol, substance abuse, partner issues, and social deprivation have also been associated with repeat TOP (Fisher et al., 2005; Heikinheimo et al., 2008; John et al., 2005; Prager et al., 2007). A recent study from Scotland (Mccall et al., 2016) found that younger age less than 20 years was linked with repeat TOP (OR 5.59, 95% CI 4.17-7.49), which is supported by findings of other studies (Heikinheimo et al., 2008; Mentula et al., 2010; Rose et al., 2015). Earlier studies highlighted that the use of intra-uterine contraception at or after the initial TOP was associated with reduced risk of repeat TOP (Heikinheimo et al., 2008; Mccall et al., 2016; Rose et al., 2015). A number of studies highlighted that the use of long-acting reversible contraception after TOP is an effective approach in reducing repeat TOP; however, discontinuation rate of contraception might be high (Heikinheimo et al., 2008; Rose et al., 2015; Rose & Lawton, 2012). Thus, it can be postulated that any contraception initiated immediately after the TOP can prevent the need for subsequent TOPs to some extent (Heikinheimo et al., 2008; Li et al., 2021).

Few studies considered how the method of TOP and gestational age at the time of TOP influence the risk for repeat TOP. A previous study from Finland reported no difference in risk of repeat TOP by method used in TOP (Niinimäki et al., 2009).

However, a recent study reported an association between surgical TOP and reduced risk of repeat TOP (OR 0.85, 95% CI 0.77-0.94) (Mccall et al., 2016). A Finnish study looked at the risk of repeat TOP by gestational age and reported that second trimester TOP was associated with repeat TOP (HR 1.4, 95% CI 1.3-1.6) and also for repeat TOP during the second trimester (HR 3.8, 95% CI 2.9-5.1) (Mentula et al., 2010).

2.5 Summary of literature review

TOP is a common gynaecological procedure worldwide and the number of TOPs is increasing all over the world annually. The influence of TOP on future birth is very important to ensure the health of infants and mothers. There are many studies examining the association between TOP and subsequent birth outcomes such as preterm birth, low birth weight, small for gestational age (SGA) birth and perinatal death, but the results are conflicting. Previous studies reported the increased risk of preterm birth and low birth weight after TOP, some studies were showing dose-response effect as well. Very few studies have been conducted on the SGA with regards to TOP. Of them, only few reported the association of TOP with SGA. Similarly, a couple of studies has been done regarding TOP and perinatal death and reported no or very small risk of perinatal death after TOP.

The use of the medical procedure for terminating a pregnancy is rapidly increasing in many countries. This has been an issue as to whether medical TOP increases the risk of future birth outcomes in comparison with surgical TOP. In addition, the timing of TOP or gestational age at TOP is another concern which possibly have several adverse birth outcomes in following births. Many previous studies have their limitations and did not have complete information on the history of TOP including number, method and gestational age at TOP. Therefore, there is a need for large population-based studies exploring the consequences of prior TOP on future birth outcomes to ensure the health of women and infants. Furthermore, most of the women undergoing TOP are of younger age, and they are more likely to repeat the procedure in later life. Repeat TOPs might be associated with adverse health risks in subsequent pregnancy; however, TOP cannot be completely avoided. Thus, knowledge on possible factors influencing repeat TOP is crucial in reducing the need for repeat TOP.

3 AIMS OF THE STUDY

The main aim of this study was to investigate the effects of previous termination of pregnancy (TOP) on subsequent birth outcomes among first-time mothers with singleton births in Finland using national register data.

The specific aims of the study were as follows:

1. To compare the effects of medical and surgical termination of pregnancy (TOP) on the risk of preterm birth, low birth weight, small for gestational age and perinatal death in subsequent births. (Sub-study I)

2. To assess the risk of preterm birth, small for gestational age births, and perinatal death by number and method of pre-birth termination of pregnancy (TOP). (Sub-study II)

3. To study the consequences of prior termination of pregnancy (TOP) on preterm birth, low birth weight, small for gestational age, and perinatal death on subsequent birth by gestational age at the time of TOP. (Sub-study III)

4. To assess how sociodemographic factors, termination of pregnancy factors and contraception affects the risk of repeat termination of pregnancy (TOP). (Sub-study IV)

4 MATERIAL AND METHODS

4.1 Registers used in the study

The Medical Birth Register and the Register of Induced Abortions were used in all four studies. The linked Medical Birth Register and the Register of Induced Abortions were used in the sub-studies I, II and III and the Register of Induced Abortions was used in the sub-study IV.

4.1.1 Register of Induced Abortions

The Finnish Institute for Health and Welfare (THL) has maintained the Finnish Register of Induced Abortions. In Finland, the Abortion Register was started in 1950 but computerized data on all TOPs have been available since 1983. Physicians are required to report TOP to the Register of Induced Abortions using a specific form. The register covers the information on women's background such as age, occupation, residence, marital status, and the information on recent pregnancy termination such as method of TOP, indications for TOP, gestational age at TOP, date of TOP, and the use of contraception before and after TOP.

4.1.2 Medical Birth Register

The Finnish Institute for Health and Welfare (THL) maintains the Finnish Medical Birth Register, which was established in 1987. The register was reformed in 1991, 1996, 2004 and 2017 with the aim of improving the reliability of the register. The register contains information on live births, and stillbirths with a birth weight of at least 500 g, or with gestational age of at least 22 weeks. Data regarding each pregnancy and delivery is collected using a specific form containing information on the mother's background, previous pregnancy, delivery history, current pregnancy, delivery, and on infants by the age of 7 days or at discharge.

4.2 Study population

4.2.1 Sub-study I

All the mothers having had their first singleton birth during the years 1996-2013 (n=419 879) were identified from the Finnish Medical Birth Register. Those women were linked to the Register of Induced Abortions using the women's identification number to identify those who had had prior TOP. The mothers were divided into four groups according to the history and method of the TOP; no prior TOP, medical TOP, surgical TOP, and both (medical and surgical TOP). Medical TOP included those TOP(s) that were performed using mifepristone followed by misoprostol. Surgical TOPs included TOP(s) performed using either dilation or curettage or vacuum evacuation. Women who had used both medical and surgical method at TOP(s) were assigned in both group. The both group includes women either with single TOP who had used medical followed by surgical TOP or with multiple TOPs who had used medical or surgical TOP in each termination.

4.2.2 Sub-study II

All the mothers having had their first birth during the period 1996-2013 (n=419 879) were identified from the Medical Birth Register and linked to the Register of Induced Abortions to determine the history of TOP. The study population were first categorized by the number of TOPs as no TOP, one TOP, two TOPs, and more than two TOPs. Those who had history of TOP were further categorized by the method used for the TOP as medical, surgical and both (medical and surgical) group. TOPs performed using mifepristone followed by misoprostol were included in medical TOP group. TOPs performed using either dilation or curettage or vacuum evacuation were included in surgical TOP group. Women who had used both medical and surgical method at TOP(s) were assigned in both group which is explained in Sub-Study I.

4.2.3 Sub-study III

All the first-time mothers with a singleton birth were identified from the Finnish Medical Birth Register. The TOP history of those women was identified through the

linkage of the Medical Birth Register and the Register of Induced Abortions. The information on gestational age at TOP, interpregnancy interval, gestational age at birth and birth weight was missing in a very small proportion, which were removed from the dataset and a total of 418 690 women were included in the study. The women were classified according to the gestational age at the time of TOP as early and late TOP. TOPs performed before 12 weeks were assigned in early TOP group and TOPs performed at 12 or more weeks gestation were assigned in late TOP group. Since most of the TOPs were performed before 12 gestation weeks, the study population was further categorized into four groups for additional analysis: no prior TOP; TOP before 8 gestational weeks; TOPs performed from 8 and 12 gestational weeks; and TOPs after 12 gestational weeks.

4.2.4 Sub-study IV

All the TOPs (n=368 981) during the period 1987-2015 were identified from the Finnish Register of Induced Abortions. TOPs missing the woman's personal identification code (1.7%); TOPs missing the exact date of procedure (17.8%) which were mostly from the earlier years; TOPs with erroneous history (13.4%); and TOPs with foetal indications (1.8%) were excluded from the dataset (Figure 6). Finally, a total of 193 741 women having had TOP were included in the study. The women were classified according to the number of TOP as follows: no repeat TOP (those with only one TOP, 78.8%); one repeat TOP (two TOPs, 15.5%); two repeat TOPs (three TOPs, 4%); three repeat TOPs (four TOPs, 1.2%); four repeat TOPs (five TOPs, 0.4%); and finally five or more repeat TOPs (more than five TOPs, 0.2%).

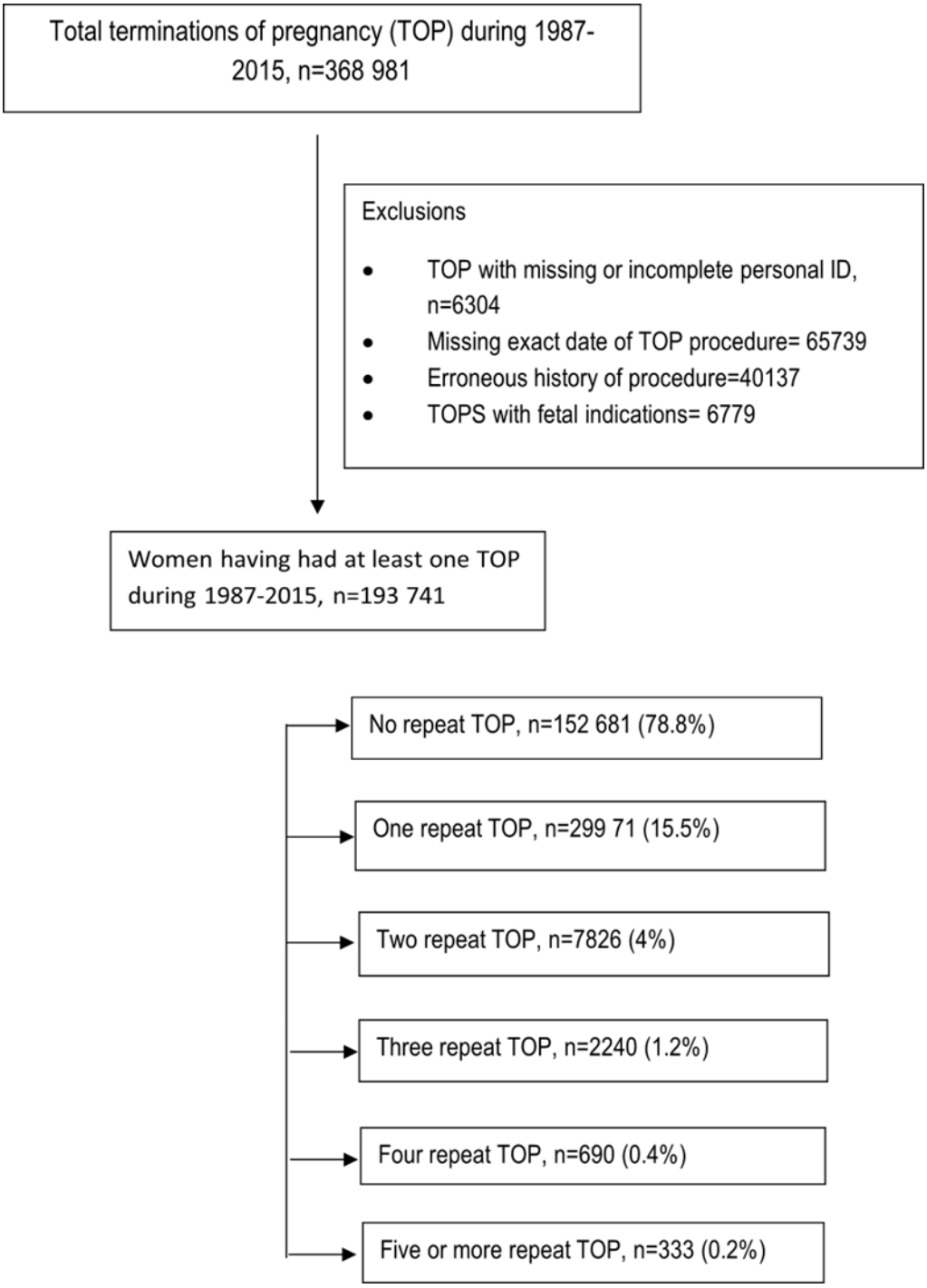

Figure 6. Flow chart of study subjects, Sub-study IV

4.3 Study design and variable description

The study design for all the four sub-studies were register-based cohort studies and sub-studies I-III were retrospective in nature. A summary of aim, study design, data source and study periods are shown below (Table 6).

Table 6. Summary of aim, study population, data source and study design of sub-studies I-IV

	Aim	**Study design**	**Data source**	**Study period**
Sub-study I	To compare the effects of medical and surgical TOP on the risk of preterm birth, low birth weight, small for gestational age, and perinatal death in subsequent birth.	Register based cohort study	Medical Birth Register Register of Induced Abortions	1996-2013
Sub-study II	To assess the risk of preterm birth, perinatal death and small for gestational age births by number and method of pre-birth TOP.	Register based cohort study	Medical Birth Register Register of Induced Abortions	1996-2013
Sub-study III	To study the consequences of prior TOP on preterm birth, low birth weight and small for gestational age on following birth by gestational age at the time of TOP.	Register based cohort study	Medical Birth Register Register of Induced Abortions	1996-2013
Sub-study IV	To assess how sociodemographic factors, TOP factors and contraception affects the risk of repeat termination of pregnancy	Register based cohort study	Register of Induced Abortions	1987-2015

4.3.1 Sub-study I

The women included in the study were divided according to their history and method of TOP. They were divided into four groups: no prior TOP (n=365 356); medical TOPs only (n=13 450); surgical TOPs only (n= 38 659); and both types of TOPs.

The outcomes studied were preterm birth, low birth weight, small for gestational age and perinatal death. The risks for these outcomes were compared among the medical or surgical group with no prior TOP group (no TOP as reference) and the surgical and medical group (medical TOP as reference). The number of women in both group is very few for analysis and thus excluded in the logistic regression analysis.

The gestational age at birth, birth weight, and perinatal death was retrieved from the Medical Birth Register. Preterm birth was divided into three categories: extremely preterm, very preterm and preterm birth. The birth was defined as preterm if the gestational age at birth was less than 37 weeks, very preterm if the gestational age at birth was less than 32 weeks and extremely preterm if the gestational age at birth was less than 28 weeks. The births were defined as normal that occurred at 37 or more gestation weeks and were treated as the reference group. Similarly, the birth weight of less than 2500 grams was defined as low birth weight and birth weight less than 1500 grams was defined as very low birth weight. Small for gestational age (SGA) was defined according to sex-specific Finnish standards for newborn infants between 24 and 43 gestational weeks. Newborns were defined as SGA if the birth weight was below the mean -2SD compared with the expected weight for the same gestational age and sex infants. Perinatal death was defined as the sum of stillbirths (deaths referring from 22 weeks gestation) and early neonatal deaths (until the end of the first week after birth).

The background characteristics of mothers such as mother's age, marital status, residence and smoking during pregnancy were retrieved from the Medical Birth Register. Such information referred to the time of the birth of a baby. The mother's municipality of residence was categorized according to Statistics Finland and the categories were further grouped into urban, semi-urban, rural and abroad. The marital status in the Medical Birth Register was divided into seven categories: married and living together with spouse; registered partnership; married and living separated from spouse; never married; divorced; widowed; and unknown. These were further categorized into three groups: married/cohabiting; unmarried/single; and unknown.

4.3.2 Sub-study II

All the first-time mothers included in the study (n=419 879) were first categorized into four groups according to the number of TOPs: no prior TOP (n=365 356), one TOP (n=46 023), two TOPs (n=16 690) and more than two TOPs (n=1639). These were further categorized on the basis of the method used in prior TOP: no prior TOP, one TOP (either one medical or one surgical TOP), two TOPs (either two medical or two surgical TOPs or one medical and one surgical TOP), and more than two TOPs (either of more than two medical, more than two surgical or more than two both types of TOPs i.e medical and surgical). In this study, the risks of different birth outcomes were compared among different groups with multiple TOPs (more than one surgical TOP vs more than one medical TOP, more than one medical TOP vs one medical TOP, more than one surgical TOPs vs one surgical TOP).

The outcomes measures such as preterm birth, perinatal death and small for gestational age were retrieved from the Medical Birth Register and they were defined as in Sub-study I. The background characteristics of mothers were also retrieved from the Medical Birth Register and defined in Sub-study I.

4.3.3 Sub-study III

The mothers included in the study were divided in three groups according to the gestational age at TOP: no prior TOP (n=364 392), early TOP (n=46 589) and late TOP (n=7709). No prior TOP included women with no prior history of TOP; early TOP included women who had TOP before 12 weeks of gestation; and late TOP included women who had TOP at 12 or more weeks of gestation. In cases where data was missing regarding gestational age at birth, birth weight, gestational age at TOP and interpregnancy interval, these were excluded from the dataset though the proportion was very low.

The risk of birth outcomes such as preterm birth, low birth weight, SGA and perinatal death were compared among the early or late TOP vs no prior TOP group and late TOP vs early TOP. The outcomes were retrieved from the Medical Birth Register using gestational age at birth, birth weight and perinatal death, which were defined in the Sub-study I. Information on background characteristics were retrieved from the Medical Birth Register (explained in Sub-study I). Similarly, information

regarding TOP histories, procedures, numbers and gestational weeks at TOP were retrieved from the Register of Induced Abortions.

4.3.4 Sub-study IV

In the sub-study IV, the women having had more than one TOP were assigned in repeat TOP group and those having only one TOP were assigned in no repeat TOP group. The women with more than one (repeat) TOP were categorized based on the number of TOPs as: no repeat TOP, one repeat TOP, two repeat TOPs, three repeat TOPs, four repeat TOPs, and more than five repeat TOPs to estimate the risk of repeat TOP in comparison with no repeat TOP.

The predictor variables were also identified using the Register of Induced Abortions. In this study, sociodemographic variables such as women's age, marital status, municipality of residence, and parity were used. The history of TOP such as method of TOP, gestational age at TOP, indications for TOP and contraception used before TOP were also used in this study. The urbanity of residence was classified as urban, semi-urban and rural according to Statistics Finland. The contraception used before TOP indicating the use at the time of conception was also divided into three categories based on the reliability of contraception as reliable, less reliable (depend on correctness of use) and no reliable methods. The reliable methods contained Long-acting Reversible Contraception (LARC) including intra-uterine device and implants, hormonal method and sterilization; less reliable included barrier method or condom that is based on the correctness of use; and no reliable methods included no contraception, unknown method or other methods of contraception that are rarely used. The study period was very long and included the period before medical methods were introduced. Therefore, we divided it into two periods based on the distribution of repeat TOPs over time. As the share of repeat TOPs plateaued in 2005, the time period was divided into two: 1987-2005 (during which repeat TOPs were increasing); and 2006-2015 (during which repeat TOPs stagnated). A sub-analysis was performed taking into account the most recent period from 2006-2015 using the same method as for whole study period.

4.4 Statistical methods

All the data were analysed using IBM SPSS Statistics for Windows software (IBM Corp., Armonk, NY, USA) for the study I (version 23) and IV (version 27); and STATA version 14 for the sub-studies II and III. Chi square test was used to determine the differences between groups as the variables are categorical. The differences between the groups were tested using relative tests for proportion (Sub-study III). The level of significance was set at $p<0.05$.

Binary and multinomial logistic regression analysis was performed to assess the risk of birth outcomes (Sub-studies I, II and III). The results are presented as unadjusted and adjusted ORs with 95% CI. In the sub-studies I and II, the confounders used in the logistic regression analysis were maternal background characteristics such as age, marital status, urbanity of residence, smoking during pregnancy, year of childbirth while comparing women with no prior TOP group with those with TOP history. Additional adjustments were done for the number of TOPs, gestational age at TOP, and year of last TOP as these variables are associated with adverse birth outcomes while comparing different groups with TOP histories. In the sub-study III, the confounders used in the adjusted model were age, marital status, municipality of residence, smoking during pregnancy, number of TOPs, TOP procedure and interpregnancy interval. The confounders selected were based on previous studies and the known risk factors for adverse birth outcomes as well as their availability and quality in the national registers. In Sub-studies I-III, different comparisons were done among different groups while estimating the risk of adverse birth outcomes, thus the different adjustments were done according to the comparison group. Late TOPs were performed mostly due to medical reasons; those cases were excluded when comparing late vs early TOPs.

In sub-study IV, cox proportional regression analysis was performed to estimate the risk of demographic factors, parity, and history of TOP on repeat TOP. The results were presented as hazard ratios (HR) and 95% confidence interval (CI). The risk for each repeat TOP up to four repeat TOPs was estimated with reference to no repeat TOP. All the factors were entered in the model in multivariate analysis. Kaplan-Meier curve was used to assess cumulative risk of repeat TOP over the study period.

4.5 Ethical aspects

All these register-based studies were conducted after getting approval from the ethical committee of Finnish National Institute for Health and Welfare (THL) (THL/1383/5.05.00/2009) and permission was obtained from THL (THL/1241/6.02.00/2014) and (THL/646/6.02.00/2017) to use the data.

The data from the Medical Birth Register were linked to the Register of Induced Abortions using the unique personal identification number. Privacy protection of the data was fully ensured. Only the researchers had access to the data and personal identification numbers were removed before analysis. The consent of the participants was not required while using register-based data.

5 RESULTS

5.1 Sociodemographic characteristics of study population

The sub-studies I, II and III included a total number 419 879 first-time Finnish mothers with a singleton birth during the years 1996-2013. Of them, 87% had no history of prior TOP, 11% had only one TOP, 1.6 % had two TOPs, and 0.4% had more than two TOPs. The mean age of mothers was 27.39 (SD 5.23) years (Table 7). The mothers with prior TOP were more often younger, single, urban residents and smokers than the mothers without a history of prior TOP (Table 7). Among the mothers having had previous TOP (n=54 523), 70.9% had surgical TOP, 24.7% had medical TOP, and 4.4% had both medical and surgical TOP. Compared with the mothers with medical TOP, a higher number of TOPs were found among mothers with surgical TOP, and the TOPS were performed mostly before the year 2000. Likewise, almost 86% of TOPS were performed before the 12 weeks of gestation, while 14% were performed at or after 12 weeks of gestation.

In the sub-study IV, a total of 193 741 women who had gone through TOP during 1987-2015 were included. Among them, 78.8% had only one TOP, 15.5% had two TOPs, and 5.7% had three or more TOPs. Younger women, single or unmarried, and women residing in urban areas had a higher number of repeat TOPs.

Table 7. Background characteristics of Finnish first-time mothers in 1996-2013 by the history of terminations of pregnancy (TOPs)

Maternal characteristics	No prior TOP % (n=365356)	One TOP % (n=46023)	Two TOPs % (n=6861)	More than two TOPs % (n=1639)	Total % (n=419879)	P-value*
Age						
Mean (SD)	27.35(5.18)	27.58(5.35)	27.93(5.60)	28.74(5.33)	27.39(5.23)	
≤19	5.8	5.8	4.0	1.9	5.8	<0.001
20–24	24.5	26.1	26.8	22.1	24.7	
25–29	36.9	32.4	31.8	34.7	36.3	
30–34	23.6	23.9	23.8	26.5	23.7	
35–39	7.7	9.6	10.9	11.4	7.9	
≥40	1.5	2.2	2.7	3.4	1.6	
Residence						
Urban	71.1	72.8	75.8	77.7	71.4	<0.001
Semi-urban	14.2	13.7	12.1	11.5	14.1	
Rural	14.1	13.0	11.6	10.3	13.9	
Abroad	0.6	0.4	0.4	0.4	0.6	
Marital status						
Married/cohabiting	87	79.7	74.9	72.1	85.9	<0.001
Unmarried/single	12.8	20.1	24.9	27.6	13.8	
Others	0.3	0.2	0.2	0.3	0.3	
Smoking status						
No smoking	82.7	68	56.7	50.7	80.5	<0.001
Quitted smoking	4.8	7.7	9	11.1	5.2	
Smoked through pregnancy	10.5	22.2	31.8	35.8	12.3	
Others	2.0	2.1	2.5	2.4	2	

*P-value from chi-square test and statistical significance at the level of 0.05

5.2 Termination of pregnancy and perinatal outcomes by their method (Sub-study I)

Figure 7 shows the incidence (per 1000 births) of different perinatal outcomes among first-time Finnish mothers according to their prior TOP and the method of TOP. Incidence of preterm birth, low birth weight and SGA birth was high in all study groups: women with no prior TOP, women having had medical TOP, surgical TOP, and both medical and surgical TOPs. Among the mothers with previous medical TOP, the incidence of very preterm birth, preterm birth, very low birth weight and low birth weight was lower than surgical TOP group (Figure 7).

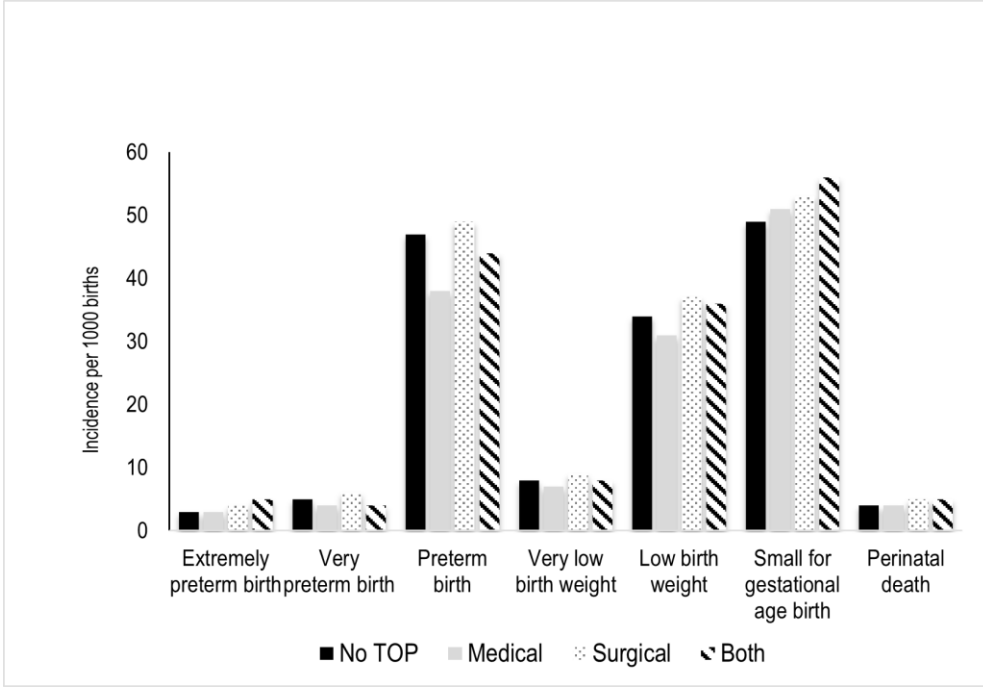

Figure 7. Incidence of perinatal outcomes among first-time Finnish mothers in 1996-2013 by prior TOP and the method of TOP

The unadjusted analysis showed higher risk of extremely preterm birth, very preterm birth, preterm birth and low birth weight among the mothers with surgical TOPs compared with those with no history of TOP (Table 8). The increased risk for adverse outcomes did not remain significant after adjusting for background characteristics such as age, marital status, residence, smoking status of mothers, and year of childbirth (Table 8). However, mothers with surgical TOPs had marginally increased risk for SGA compared with the mothers with no TOPs. After adjusting for the demographic factors, the mothers with previous medical TOPs had decreased risk for preterm birth and low birth weight when compared with mothers with no previous TOPs (Table 8).

Increased risk for preterm birth and low birth weight was found after surgical TOPs than after medical TOPs, when adjusted for sociodemographic characteristics (Table 8). The risk of preterm birth and low birth weight remained significant, even after the additional adjustment for the number of previous TOPs, gestational age at the time of TOP, and year of the last TOP (Table 8). When the analysis was restricted to those mothers having had only one TOP adjusting for the same confounders excluding number of TOP, the results remained still significant. Increased risk for preterm birth and low birth weight was found after one previous surgical TOP than after one previous medical TOP (Table 8).

Table 8. Crude and adjusted ORs and 95% confidence intervals for perinatal outcomes of first-time Finnish mothers in 1996-2013 according to the method of TOP

Perinatal outcomes	Medical vs no TOP[1]	Surgical vs no TOP[1]	Surgical vs medical TOP[2]	Surgical vs medical TOP, only one TOP[3]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Extremely preterm birth <28 weeks				
Crude Model	0.91 (0.66-1.26)	1.30 (1.10-1.54)	1.43 (0.99-2.04)	1.32 (0.91-1.92)
Adjusted Model I	0.94 (0.68-1.30)	1.16 (0.98-1.38)	1.20 (0.79-1.81)	1.12 (0.73-1.73)
Adjusted Model II			1.43 (0.90-2.30)	1.39 (0.84-2.30)
Very preterm birth <32 weeks				
Crude Model	0.83 (0.64-1.08)	1.19 (1.04-1.37)	1.44 (1.07-1.92)	1.33 (0.98-1.80)
Adjusted Model I	0.88 (0.67-1.15)	1.03 (0.89-1.18)	1.23 (0.87-1.71)	1.13 (0.80-1.61)
Adjusted Model II			1.24 (0.85-1.81)	1.23 (0.83-1.84)
Preterm births <37 weeks				
Crude Model	0.81 (0.74-0.89)	1.05 (1.00-1.10)	1.29 (1.17-1.43)	1.26 (1.13-1.40)
Adjusted Model I	0.83 (0.76-0.91)	1.00 (0.95-1.05)	1.16 (1.03-1.30)	1.15 (1.02-1.29)

Adjusted Model II			1.19 (1.04-1.36)	1.18 (1.02-1.36)
Very low birth weight <1500 grams				
Crude Model	0.87(0.70-1.07)	1.15 (1.03-1.29)	1.33 (1.05-1.68)	1.25 (0.98-1.60)
Adjusted Model I	0.88 (0.71-1.10)	1.00 (0.89-1.12)	1.16 (0.89-1.52)	1.11 (0.84-1.47)
Adjusted Model II			1.27 (0.93-1.73)	1.27 (0.91-1.76)
Low birth weight <2500 grams				
Crude Model	0.91 (0.82-1.00)	1.10 (1.04-1.17)	1.22 (1.09-1.36)	1.21 (1.08-1.36)
Adjusted Model I	0.86 (0.78-0.95)	0.98 (0.93-1.04)	1.16 (1.02-1.32)	1.16 (1.01-1.32)
Adjusted Model II			1.16 (1.00-1.35)	1.18 (1.01-1.38)
Small for gestational age (SGA)				
Crude Model	0.96 (0.88-1.03)	0.92 (0.88-0.97)	0.96 (0.88-1.05)	0.96 (0.88-1.05)
Adjusted Model I	1.05 (0.97-1.14)	1.07 (1.02-1.12)	0.99 (0.89-1.10)	0.99 (0.89-1.10)
Adjusted Model II			1.00 (0.89-1.13)	1.01 (0.89-1.14)
Perinatal death				
Crude Model	1.03 (0.79-1.34)	0.83 (0.72-0.96)	0.81 (0.60-1.08)	0.81 (0.60-1.08)
Adjusted Model I	0.97 (0.74-1.27)	0.98 (0.85-1.14)	1.13 (0.80-1.60)	1.13 (0.80-1.60)
Adjusted Model II			1.00 (0.67-1.48)	1.00 (0.67-1.48)

Adjusted Model I- adjusted for socio demographic factors; maternal age, marital status of mothers, area of residence, smoking status, and year of childbirth

Adjusted Model II- adjusted for number of previous TOPs, gestational age at TOP, and the year of last TOP

[1] No TOP group is used as reference group

[2] Medical group is used as reference group

[3] Medical group is used as reference group and includes mothers with only one TOP

5.3 Birth outcomes after previous termination of pregnancy by their number and methods (Sub-study II)

Incidence of all birth outcomes such as extremely preterm birth, very preterm birth, preterm birth, perinatal death, and SGA after surgical TOP increased with the additional number of TOPs (Figure 8). However, an increased incidence was found only for SGA after medical TOP (Figure 8).

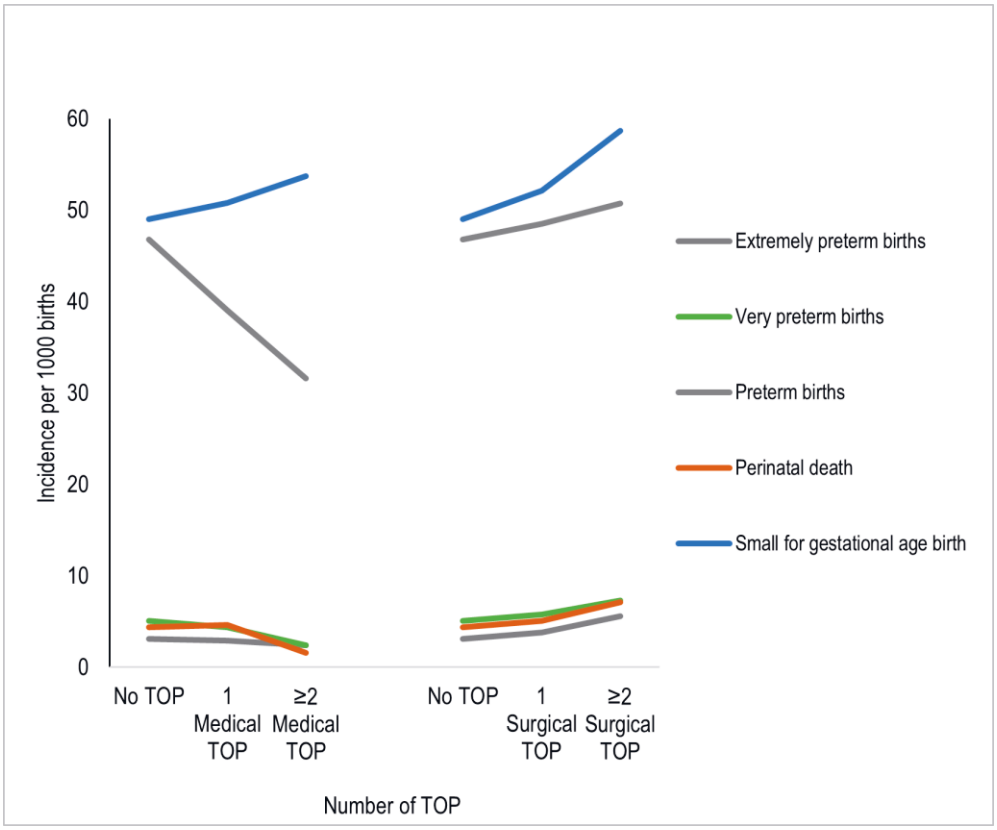

Figure 8. Incidence of perinatal outcomes (per 1000 births) by the number and method of termination of pregnancy (TOP)

In the unadjusted result, women having had one surgical TOP had significantly higher risk for extremely preterm birth and very preterm birth compared to women with no TOP (Table 9). However, the risk remained insignificant after adjustment for confounders such as maternal age, residence, marital status, smoking status and the year of childbirth. The adjusted result showed that women with single TOP had 1.1-fold higher risk for SGA (Table 9). After adjusting for confounders, women with a history of at least two surgical TOPs had 1.5-fold higher risk for extremely preterm birth compared with the women who had no previous TOP (Table 9). Compared to women with no TOP, women with one previous medical TOP had a reduced risk for preterm birth and women with at least two medical TOPs had a lower risk for preterm birth.

Table 9. Perinatal outcomes among the first-time mothers with singleton births having previous TOPs by the number and methods of TOPs in 1996-2013 in Finland

Perinatal outcomes	One TOP vs no TOP		More than one TOPs vs no TOP	
	One medical TOP vs no TOP	One surgical TOP vs no TOP	More than one medical TOPs vs no TOP	More than one surgical TOPs vs no TOP
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Extremely preterm birth <28 weeks				
Crude model	0.93 (0.66-1.30)	1.23 (1.02-1.47)	0.76 (0.24-2.35)	1.84 (1.25-2.70)
Adjusted model[a]	0.96 (0.68-1.35)	1.11 (0.92-1.33)	0.82 (0.26-2.58)	1.51 (1.03-2.23)
Very preterm birth <32 weeks				
Crude model	0.87 (0.66-1.14)	1.16 (1.00-1.34)	0.46 (0.15-1.43)	1.45 (1.04-2.03)
Adjusted model[a]	0.92 (0.70-1.21)	1.01 (0.87-1.18)	0.50 (0.16-1.55)	1.14 (0.81-1.59)
Preterm birth <37 weeks				
Crude model	0.83 (0.75-0.91)	1.04 (0.99-1.10)	0.66 (0.48-0.91)	1.09 (0.96-1.25)
Adjusted model[a]	0.85 (0.77-0.93)	0.99 (0.94-1.05)	0.70 (0.51-0.96)	1.00 (0.88-1.14)
Perinatal death				
Crude model				
Adjusted model[a]	0.96 (0.74-1.26)	0.87 (0.74-1.02)	2.82 (0.70-11.30)	0.63 (0.44-0.88)
	0.91 (0.69-1.19)	1.02 (0.87-1.19)	2.52 (0.63-10.10)	0.82 (0.58-1.16)
Small for gestational age birth (SGA)				
Crude model	0.96 (0.88-1.04)	0.94 (0.89-0.98)	0.91 (0.71-1.16)	0.82 (0.73-0.93)
Adjusted model[a]	1.05 (0.97-1.15)	1.07 (1.02-1.13)	1.05 (0.82-1.34)	1.07 (0.95-1.21)

Adjusted model[a] - adjusted for maternal characteristics (maternal age, marital status, maternal smoking, maternal residence of municipality and birth year of child).

In the unadjusted analysis, higher risk for several perinatal outcomes were observed while comparing women with a history of repeat surgical TOPs and both types of TOPs to those with repeat medical TOPs; however, the risks were statistically not significant (Table 10). Even after the adjustment for maternal characteristics, gestational age at TOP and the year of last TOP, the risks were insignificant. While analysing separately for medical and surgical TOP method, no increased risk was seen after repeat TOPs compared with single TOP (Table 10).

Table 10. Perinatal outcomes among women with the first birth after previous repeat medical, surgical or both medical and surgical TOPs in Finland during 1996-2013

Perinatal outcomes	More than one surgical TOPs vs more than one medical TOPs	More than one both TOPs (medical and surgical) vs more than one medical TOPs	More than one medical TOPs vs one medical TOP	More than one surgical TOPs vs one surgical TOP
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Extremely preterm birth <28 weeks				
Crude model	2.43 (0.74-8.04)	1.96 (0.54-7.02)	0.81 (0.25-2.65)	1.50 (0.99-2.27)
Adjusted model[a]	1.06 (0.25-4.39)	0.95 (0.24-3.74)	1.09 (0.33-3.66)	1.35 (0.88-2.07)
Very preterm birth <32 weeks				
Crude model	3.15 (0.97-10.28)	1.78 (0.49-6.47)	0.53 (0.16-1.69)	1.25 (0.87-1.80)
Adjusted model[a]	1.74 (0.43-7.02)	1.18 (0.30-4.65)	0.60 (0.18-1.97)	1.09 (0.76-1.58)
Preterm birth <37 weeks				
Crude model	1.65 (1.17-2.32)	1.40 (0.97-2.03)	0.80 (0.58-1.11)	1.05 (0.91-1.21)
Adjusted model[a]	1.21 (0.79-1.86)	1.24 (0.84-1.83)	0.81 (0.58-1.12)	1.03 (0.89-1.18)
Perinatal death				
Crude model	0.22 (0.05-0.93)	0.29 (0.06-1.29)	2.92 (0.71-11.98)	0.72 (0.50-1.04)
Adjusted model[a]	0.44 (0.09-2.22)	0.51 (0.41-9.41)	2.72 (0.65-11.32)	0.86 (0.59-1.25)
Small for gestational age birth (SGA)				
Crude model	0.91 (0.69-1.19)	0.29 (0.06-1.29)	1.06 (0.82-1.37)	1.13 (0.99-1.29)
Adjusted model[a]	1.25 (0.87-1.80	0.51 (0.11-2.42)	0.98 (0.75-1.27)	0.98 (0.86-1.12)

Adjusted model[a] - adjusted for maternal characteristics (maternal age, marital status, maternal smoking, maternal residence of municipality and year of birth), gestational age at TOP and year of last TOP.

5.4 Perinatal outcomes after termination of pregnancy according to the gestational age at termination (Sub-study III)

The incidence of preterm birth, low birth weight, and SGA birth in subsequent birth after previous TOP were high in all study groups according to gestational age at TOP. Increased incidence of adverse birth outcomes was seen more often among women with late TOP than women with no TOP and early TOP (Figure 9).

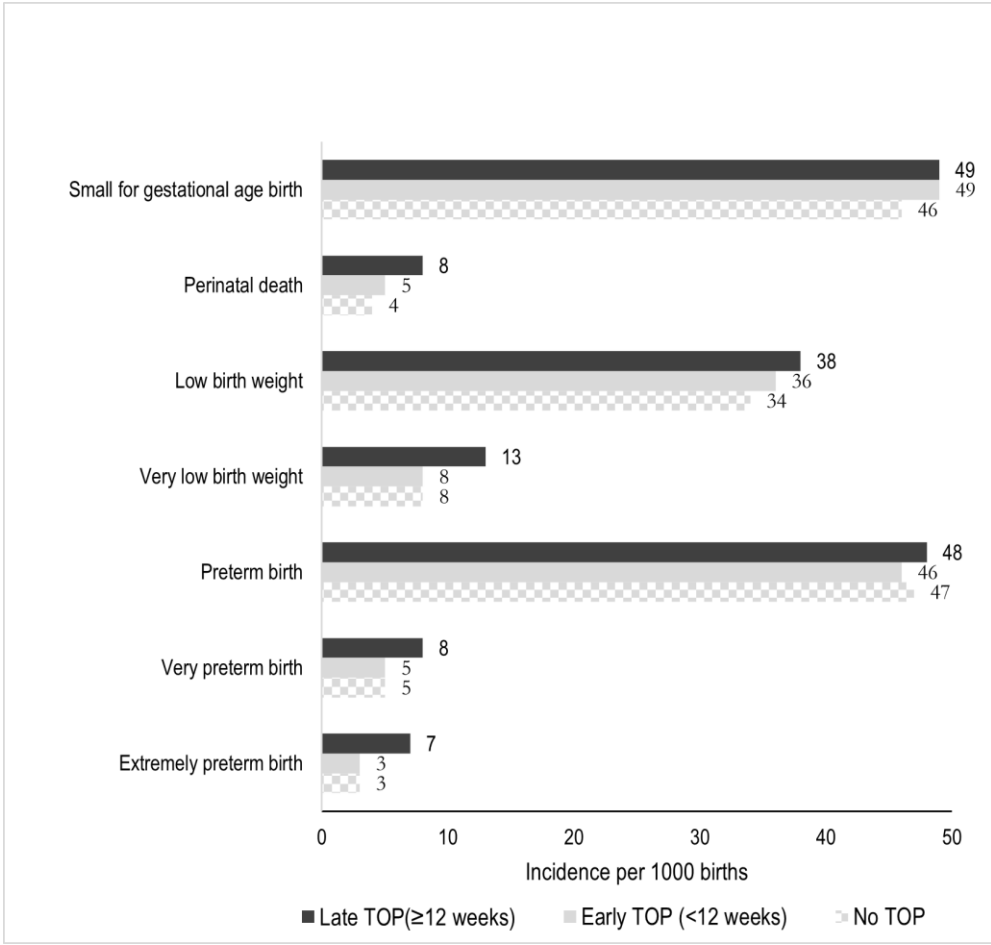

Figure 9. Incidence of birth outcomes according to gestational age at previous termination of pregnancy (TOP) in Finland during the years 1996-2013

A slight but increased risk of having a small for gestational age birth was found among women who had early TOP compared with women having had no TOP after adjusting for maternal characteristics (Table 11). Women having had late TOP showed significantly increased risk for extremely preterm birth, very preterm birth, very low birth weight and small for gestational age birth and a significantly decreased risk for perinatal death, as compared with those having had no TOP (Table 11).

Women having had late TOP had significantly increased risk for extremely preterm birth (OR 2.28, 95% CI 1.53-3.39) and very low birth weight (OR 1.62, 95% CI 1.22-2.16) compared to women having had early TOP, after adjustment for confounders such as maternal characteristics, number and method of TOP and interval between pregnancies (Table 11). When analysis was limited to women having had only one TOP, significantly increased risk for extremely preterm birth after late TOP was found (Table 11). Compared to women with two or more early TOPs, those with two or more late TOPs had significantly higher risk for extremely preterm birth (OR 4.09, 95% CI 2.05-8.18) and very low birth weight (OR 2.65, 95% CI 1.61-4.35) (Table 11). A significant reduction in the risk for perinatal death was found among women with late TOP and two or more late TOPs when compared with those with early TOP and two or more early TOPs.

A sub-analysis was performed separately for those TOPs that were performed medically and surgically. Significantly increased risk was found for preterm birth and low birth weight among women having had a late medical TOP compared with women who had an early medical TOP, after adjusting for confounders. Similarly, women having had late surgical TOP had 2.6- and 1.5-fold increased odds of extremely preterm birth and very low birth weight compared with women having had early surgical TOP (Table 12). Another sub-analysis was done by classifying gestational weeks into three groups such as <8 weeks, 8-12 weeks and $\geq$13 weeks. Higher risk for extremely preterm birth and very low birth weight was found among women having had TOP at 13 or more weeks of gestation compared with women having had TOP before 8 weeks of gestation, after adjustment for confounders (Table 12).

Table 11. Risks of adverse birth outcomes by gestational weeks at previous termination of pregnancy (TOP) among first-time Finnish mothers during 1996–2013

Birth outcomes	Early TOP vs no TOP		Late TOP vs no TOP		Late vs early TOP[1]		One late vs one early TOP[1]		≥2 late vs ≥2 early TOP[1]	
	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[b]	Crude	Adjusted[c]	Crude	Adjusted[c]
	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)
Extremely preterm birth <28 weeks	1.04(0.87-1.23)	0.97(0.82-1.16)	2.29(1.75-3.02)	2.06(1.56-2.73)	1.88(1.30-2.73)	2.28(1.53-3.39)	1.41(0.86-2.32)	1.71(1.02-2.81)	2.93(1.53-5.60)	4.09(2.05-8.18)
Very preterm birth <32 weeks	1.00(0.87-1.14)	0.91(0.79-1.05)	1.63(1.27-2.09)	1.46(1.13-1.88)	1.33 (0.93-1.88)	1.37(0.95-1.99)	1.27(0.83-1.95)	1.27(0.81-1.99)	1.40(0.73-2.67)	1.69(0.86-3.33)
Preterm birth <37 weeks	0.97(0.93-1.02)	0.95(0.90-0.99)	1.04(0.93-1.15)	1.00(0.90-1.11)	1.04 (0.91-1.18)	1.05(0.91-1.20)	1.04(0.89-1.22)	1.05(0.90-1.24)	1.02(0.79-1.30)	1.02(0.79-1.32)
Very low birth weight 1500 grams	0.98(0.87-1.09)	0.89(0.79-1.00)	1.71(1.39-2.09)	1.50(1.22-1.84)	1.49 (1.13-1.96)	1.62(1.22-2.16)	1.21(0.85-1.73)	1.28(0.89-1.86)	2.05(1.28-3.29)	2.65(1.61-4.35)
Low birth weight 2500 grams	1.04(0.99-1.10)	0.94(0.90-1.00)	1.11(0.98-1.24)	0.97(0.86-1.09)	1.07 (0.93-1.24)	1.07(0.92-1.24)	1.07(0.90-1.28)	1.10(0.92-1.31)	1.03(0.79-1.36)	0.99(0.75-1.32)
Perinatal death	0.95(0.82-1.09)	1.05(0.91-1.21)	0.56(0.43-0.74)	0.64(0.49-0.84)	0.60 (0.43-0.83)	0.55(0.39-0.78)	0.73(0.48-1.12)	0.74(0.48-1.16)	0.40(0.22-0.72)	0.30(0.16-0.56)
Small for gestational age (SGA)	0.93(0.89-0.97)	1.06(1.01-1.11)	0.94(0.85-1.05)	1.13(1.02-1.25)	0.96 (0.85-1.08)	1.03(0.90-1.17)	1.05(0.90-1.23)	1.10(0.94-1.29)	0.85(0.68-1.06)	0.88(0.71-1.11)

Adjusted[a]: Adjusted for maternal age, maternal residence, marital status and maternal smoking status.

Adjusted[b]: Adjusted for maternal age, residence, maternal smoking status, method of TOP, number of TOP and interval between pregnancies.

Adjusted[c]: Adjusted for maternal age, residence, maternal smoking status, method and interval between the pregnancies.

[1]Analysis was performed excluding those women whose induced abortion was performed due to medical indications.

Table 12. Risk for adverse birth outcomes by gestational age and method of termination of pregnancy (TOP) among first-time Finnish mothers in 1996-2013

Birth outcomes	Early and late TOP by the method[a]				TOP at different gestational age vs <8 weeks of gestation[c]			
	Late vs early medical TOP		Late vs early surgical TOP		8-12 weeks vs <8 weeks of gestation		≥13 weeks vs <8 weeks of gestation	
	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	Crude OR (95% CI)	Adjusted[d] OR (95% CI)	Crude OR (95% CI)	Adjusted[d] OR (95% CI)
Extremely preterm birth <28 weeks	1.76 (0.75-4.14)	1.62 (0.64-4.12)	2.15 (1.38-3.34)	2.61 (1.67-4.09)	1.56 (1.02-2.40)	1.28 (0.79-2.06)	2.35 (1.27-4.36)	2.83 (1.44-5.55)
Very preterm birth < 32 weeks	1.55 (0.76-3.15)	1.58 (0.77-3.24)	1.31 (0.84-2.04)	1.26 (0.79-2.01)	1.25 (0.89-1.73)	1.05 (0.73-1.50)	1.26 (0.71-2.23)	1.36 (0.75-2.46)
Preterm birth <37 weeks	1.49 (1.19-1.88)	1.43 (1.13-1.81)	0.89 (0.74-1.06)	0.88 (0.73-1.06)	1.07 (0.97-1.20)	0.97 (0.86-1.09)	1.11 (0.92-1.35)	1.11 (0.91-1.36)
Very low birth weight <1500 grams	1.82 (1.06-3.12)	1.73 (0.99-3.01)	1.42 (1.00-2.02)	1.51 (1.05-2.16)	1.26 (0.96-1.64)	1.04 (0.77-1.39)	1.67 (1.09-2.56)	1.79 (1.14-2.81)
Low birth weight <2500 grams	1.45 (1.13-1.87)	1.43 (1.11-1.85)	0.89 (0.73-1.10)	0.88 (0.71-1.08)	1.09 (0.97-1.23)	1.01 (0.88-1.15)	1.06 (0.85-1.32)	1.05 (0.83-1.32)
Perinatal death	0.49 (0.27-0.92)	0.51 (0.27-0.98)	0.61 (0.40-0.93)	0.57 (0.37-0.88)	0.96 (0.70-1.32)	1.13 (0.79-1.61)	0.63 (0.38-1.05)	0.62 (0.36-1.06)
Small for gestational age (SGA)	1.02 (0.81-1.27)	1.12 (0.89-1.41)	1.03 (0.87-1.22)	1.07 (0.90-1.28)	0.95 (0.86-1.05)	0.99 (0.89-1.11)	0.92 (0.76-1.10)	1.03 (0.85-1.24)

[a]Analysis performed among the women having had only one TOP.

[b]Adjusted for maternal age, maternal residence, maternal smoking and interpregnancy interval.

Missing cases for interpregnancy interval (n=3,964 (7.3%)) were excluded during the analysis.

[c]Analysis performed among the women having had TOP at different gestational age, where gestational week <8 weeks was treated as a reference for each studied group.

[d]Adjusted for maternal age, residence, smoking, number of TOP, method of TOP and interval between the pregnancies.

Missing cases for interval between the pregnancies (n=3,964 (7.3%)) were excluded during the analysis.

Analysis was performed excluding those women whose TOP was performed due to medical indications

5.5 Factors affecting risk of repeat termination of pregnancy (Sub-study IV)

The median time difference between the TOPs ranged between 2.08 and 3.83 years. 7% repeat TOPs were performed within less than 1 year of first TOP, 46% within a 1 to 5 years period and 37% were performed after 5 years. Repeat TOPs, particularly two or more repeat TOPs were markedly higher in the recent time period, 2006-2015. In the Kaplan-Meier analysis, the proportion of repeat TOPs (one vs two TOPs) was shown in 5 years' time intervals between TOPs performed during 1987-2015. The proportion of repeat TOP was higher among young women in shorter time difference between TOPs (Figure 10).

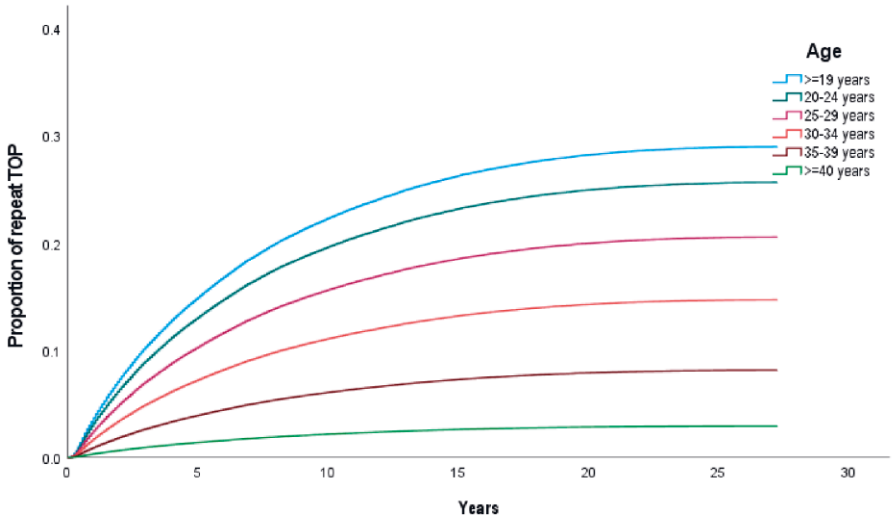

Figure 10. Risk for repeat TOP according to different age category in Finland during 1987-2015

Table 13 presents hazard ratios and 95% CI to estimate the risk of repeat TOP. Women aged more than 19 years old had a reduced risk of one repeat TOP

compared with the women aged less than 20 years (Table 13). Similar results were observed in women with two, three or four repeat TOPs compared with no repeat TOP. Being married or cohabiting was found to be a protective factor of one repeat TOP (adjusted HR 0.80, 95% CI 0.77-0.83) (Table 13). Similarly, lower risk was seen among married or cohabiting when comparing women having had two or three repeat TOPs compared to those with no repeat TOP (Table 13). Women residing in semi-urban and rural areas had a decreased risk of repeat TOPs than those residing in urban areas when comparing women with one, two, three and four repeat TOPs with those with no repeat TOP. Moreover, all the adjusted risk of repeat TOP were higher among parous women than non-parous women (HR 1.67, 95% CI 1.26-1.33).

Compared with surgical TOP, medical TOP had higher risk of repeat TOP (HR 1.30, 95% CI 1.26-1.33) (Table 13). Even increased risk was found in the additional number of repeat TOPs with reference to the no repeat TOP. Non-significant risk of one repeat TOP was found among women having had TOP after 12 weeks than those having had the TOP at or before 12 weeks. However, women having had the TOP after 12 weeks had reduced risk of having an additional repeat TOP with reference to those with only one TOP. Compared with women using a reliable method of contraception, women using less reliable contraception or no reliable contraception before the TOP had a higher risk of one repeat and two repeat TOPs with reference to no repeat TOP. However, significance was lost for three and four repeat TOPs comparing less reliable contraception with reliable contraception.

In the sub-analysis on women having had TOPs in the recent time period 2006-2015, the adjusted results were similar for the demographic factors and parity, as in the results from whole study period 1987-2015 (Table 14). However, there was a difference with regards to TOP related factors and contraception. No association was seen for the risk of all repeat TOPs compared with no repeat TOP by the TOP method (Table 14). Similarly, a slightly increased risk for one repeat TOP was found among women having had TOP after 12 gestational weeks. Non-significant risks for two, three and four repeat TOPs were found by the gestational week at TOP. As in the whole period since 1987, increased adjusted risk for one repeat TOP was found in the recent time period among women who used less reliable or unreliable method of contraception compared with women who used reliable contraception method. However, no significant

risk for more than one repeat TOPs was found for the use of contraception (Table 14).

Table 13. Adjusted Hazard Ratio and 95% Confidence Interval for repeat termination of pregnancy (TOP) among women having had TOP(s) during 1987-2015

Characteristics	One repeat TOPs vs no repeat TOP	Two repeat TOPs vs no repeat TOP	Three repeat TOPs vs no repeat TOP	Four repeat TOPs vs no repeat TOP
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age				
≤19	ref	ref	ref	ref
20–24	0.78 (0.76–0.80)	0.55 (0.52–0.59)	0.41 (0.37–0.46)	0.28 (0.23–0.34)
25–29	0.55 (0.53–0.58)	0.27 (0.25–0.29)	0.14 (0.12–0.16)	0.09 (0.07–0.12)
30–34	0.36 (0.35–0.38)	0.10 (0.09–0.12)	0.04 (0.03–0.05)	0.01 (0.01–0.03)
35–39	0.19 (0.18–0.20)	0.03 (0.03–0.04)	0.01 (0.00–0.01)	0.00 (0.00–0.01)
≥40	0.07 (0.06–0.07)	0.01 (0.00–0.01)	0.00	0.00
Marital status				
Unmarried/single	ref	ref	ref	ref
Married/cohabiting	0.80 (0.77–0.83)	0.74 (0.68–0.81)	0.68 (0.57–0.81)	0.74 (0.54–1.02)
Municipality of residence				
Urban	ref	ref	ref	ref
Semi-urban	0.87 (0.84–0.90)	0.82 (0.76–0.87)	0.75 (0.65–0.85)	0.62 (0.48–0.79)
Rural	0.83 (0.80–0.86)	0.76 (0.71–0.81)	0.62 (0.54–0.71)	0.54 (0.42–0.70)
Parity				
No	ref	ref	ref	ref
Yes	1.67 (1.61–1.72)	2.59 (2.43–2.76)	3.63 (3.23–4.08)	5.11 (4.15–6.30)
Method of TOP				
Surgical	ref	ref	Ref	ref
Medical	1.30 (1.26–1.33)	1.59 (1.51–1.68)	1.82 (1.63–2.03)	2.54 (2.07–3.17)
Gestational age at the time of TOP				
≤12 weeks	ref	ref	ref	ref
>12 weeks	0.97 (0.92–1.03)	0.86 (0.77–0.95)	0.81 (0.67–0.98)	0.69 (0.49–0.96)
Contraception before TOP				
Reliable	ref	ref	ref	ref
Reliable if used correctly	1.14 (1.06–1.23)	1.43 (1.18–1.73)	1.05 (0.73–1.51)	2.87 (0.91–9.04)
No reliable	1.33 (1.23–1.43)	1.80 (1.48–2.18)	1.39 (0.97–1.99)	4.73 (1.51–14.84)

Adjusted for each predictor variables

Table 14. Adjusted Hazard Ratio and 95% Confidence Interval for repeat termination of pregnancy (TOP) among women having had TOP(s) during 2006-2015

Characteristics	One repeat TOPs vs no repeat TOP	Two repeat TOPs vs no repeat TOP	Three repeat TOPs vs no repeat TOP	Four repeat TOPs vs no repeat TOP
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age				
≤19	ref	ref	ref	ref
20–24	0.70 (0.66-0.74)	0.51 (0.45-0.58)	0.39 (0.29-0.51)	0.30 (0.18-0.50)
25–29	0.48 (0.45-0.52)	0.29 (0.24-0.34)	0.13 (0.09-0.21)	0.16 (0.08-0.31)
30–34	0.36 (0.33-0.340	0.12 (0.07-0.16)	0.10 (0.06-0.17)	0.03 (0.01-0.12)
35–39	0.22 (0.19-0.24)	0.06 (0.04-0.08)	0.05 (0.02-0.10)	0.00
≥40	0.07 (0.05-0.09)	0.01 (0.01-0.04)	0.00	0.00
Marital status				
Unmarried/single	ref	ref	ref	ref
Married/cohabiting	0.88 (0.82-0.94)	0.81 (0.69-0.95)	0.60 (0.41-0.89)	0.88 (0.44-1.75)
Municipality of residence				
Urban	ref	ref	ref	ref
Semi-urban	0.88 (0.82-0.94)	0.81 (0.69-0.94)	1.12 (0.83-1.51)	0.50 (0.24-1.04)
Rural	0.87 (0.81-0.94)	0.93 (0.79-1.09)	0.91 (0.65-1.29)	0.73 (0.38-1.41)
Parity				
No	ref	ref	ref	ref
Yes	1.81 (1.71-1.93)	3.02 (2.65-3.44)	4.43 (3.35-5.87)	5.66 (3.43-9.35)
Method of TOP				
Surgical	ref	ref	Ref	ref
Medical	0.99 (0.93-1.06)	1.01 (0.88-1.15)	0.89 (0.68-1.16)	1.18 (0.71-1.97)
Gestational age at the time of TOP				
≤12 weeks	ref	ref	ref	ref
>12 weeks	1.11 (1.00-1.22)	1.11 (0.89-1.38)	0.98 (0.60-1.61)	0.94 (0.38-2.34)
Contraception before TOP				
Reliable	ref	ref	ref	ref
Reliable if used correctly	1.49 (1.17-1.90)	1.39 (0.79-2.47)	0.78 (0.29-2.13)	-
No reliable	1.67 (1.31-2.13)	1.66 (0.94-2.95)	0.92 (0.34-2.51)	-

Adjusted for each predictor variables

6 DISCUSSION

6.1 Summary of the key findings

In this register-based study, the first-time mothers having had prior TOP were much younger, single, urban residents and more often smokers than the mothers having had no prior TOPs (Sub-studies I, II and III). The study found that mothers with surgical TOP had higher risk for preterm birth and low birth weight compared to mothers with medical TOP (Sub-study I). Incidence of various birth outcomes such as extremely preterm birth, very preterm birth, preterm birth, perinatal death, and small for gestational age (SGA) after surgical TOP increased with the additional number of TOPs (Sub-study II). Slightly increased risk for SGA among women with a single surgical TOP and higher risk for extremely preterm birth among women with the repeat surgical TOP were found, when compared to those with no prior TOP (Sub-study II). Similarly, this study assessed the impacts of prior TOP on subsequent birth outcomes by the timing (gestational age) at TOP. Significantly increased risk of extremely preterm birth and very low birth weight was found among women with late TOP compared to women with early TOP (Sub-study III). Higher risk for extremely preterm birth and very low birth weight was found after repeat TOPs in later gestation (≥12 weeks).

Furthermore, this study also assessed the factors affecting the risk of repeat TOPs (Sub-study IV). Higher repeat TOPs were found in young, single or unmarried women, and women residing in urban areas. A higher proportion of repeat TOPs were performed within a 1-5 years' time interval. Repeat TOPs were more common among young women in a shorter time interval between TOPs. Being older, married, residing in semi-urban and rural areas, and using a reliable method of contraception were protective factors for repeat TOP; however, being parous was found to be risk factor for repeat TOPs. In the sub-analysis, considering the recent time periods after 2006, no difference in risk of repeat TOPs was found according to the method and gestational weeks at TOP except a slight and marginal increased risk for one repeat TOP according to gestation weeks.

6.2 Methodological considerations

6.2.1 Strength of the study

This population-based study covered all first-time mothers with a singleton birth from 1996-2013 and all TOPs during 1983-2013, using linked data from the Finnish Medical Birth Register and the Finnish Register of Induced Abortions (Sub-studies I, II and III). Similarly, sub-study IV contained all the TOPs performed between 1987-2015 using the Register of Induced Abortions. The data quality of the Medical Birth Register and Register of Induced Abortions are found to be very good and reliable (Gissler et al., 1995; Heino et al., 2017). A recent study showed the excellent coverage of data in the Finnish Register of Induced Abortions; 97% of TOPs were reported in the Abortion Register (Heino et al., 2017). The earlier studies also provided evidence for the completeness and accuracy of the register data comparing the medical records and the Register of Induced Abortions (Gissler et al., 1996; Heikinheimo et al., 2008). The method of TOP and gestational age recorded in the Register of Induced Abortions was reliable.

The results of the earlier studies on the effect of TOP on subsequent birth outcomes are contradictory. Many previous studies reported that prior TOP increases the risk of preterm birth and low birth weight (Bhattacharya et al., 2012; Klemetti etal., 2012; Saccone et al., 2016; Shah et al., 2009; Swingle et al., 2009; Thorp et al., 2003). However, there are some methodological constraints in some studies. Large-scale studies on the effect of previous TOP on future birth are comparatively few, and variations exists in selecting appropriate control group between different studies, and some are based on self-reported information. Only a few studies have been conducted using large datasets and there is a lack of accurate information on the number of TOPs, method of TOP, gestational age at TOP, and other possible confounders. Similarly, the information on TOP history is generally based on women's self-report, and under-reporting is likely to occur. This study is the largest one, where comparisons have been done among women with and without prior TOP; moreover, the different groups with TOP histories were compared according to TOP method, number, and gestational age at the time of the TOP. In the present study, it was possible to study different birth outcomes such as preterm births, low birth weight, small for gestational age and perinatal death according to the history of the TOPs such as number, method, and gestational age at TOP.

Various sociodemographic characteristics have been associated with TOP (Heikinheimo et al., 2008; Raatikainen et al., 2006), thus maternal age, residency, marital status and smoking were used as confounders in this study. Moreover, other factors influencing the risk for adverse birth outcomes such as year of childbirth, year of last TOP, number of TOP, method of TOP, gestational age at TOP, and interval between pregnancies were added as confounders. This study was able to control for possible confounders which were missing in some previous studies (Bhattacharya et al., 2012; Chen et al., 2004). The confounders were selected based on the previous literature, known risk factors for adverse birth outcomes and their availability and quality in the registers. Birthyear of a child was also added as one of the confounders in Sub-studies I and II. The trend in preterm birth during the years 1996-2020 is almost similar, thus addition of birthyear in the model could be an overadjustment. However, this was rechecked and found results did not differ when analyzing data either adding birthyear or removing birthyear from the model.

Several earlier studies assessing the risk factors of repeat TOP have looked for the risk of the repeat TOPs where repeat TOP was considered as having more than one TOP; and some studies have estimated the risk for second TOP with reference to the first one (Heikinheimo et al., 2009; Justad-Berg et al., 2015; Stone & Ingham, 2011). This study (Sub-study IV) is the largest one to estimate the risk for each repeat TOP compared with the no repeat TOP, covering all TOPs for a longer period 1987-2015, and TOPs for the recent period (2006-2015) in sub-analysis.

6.2.2 Limitations of the study

As TOP is a sensitive and ethical issue, it is difficult to conduct experimental studies on it. So, observational study is the most commonly used study design on this issue. However, this kind of observational studies including this study cannot infer causal relationships. Though all the first-time mothers with a singleton birth since 1996-2013 were included, some mothers might have been misclassified in the no TOP group. Because there was no information on TOPs before 1983 and TOPs performed abroad, there might be under reporting of TOP histories. However, it is assumed that such cases are very few and will be unlikely to affect the results of this study. In addition, sensitivity analysis was done including only those having first TOP and having no previous TOP; no such marked difference was found. It has

been confirmed that the methods of TOP have been accurately reported in Finnish Register of Abortions (Heino et al., 2017). However, the register did not contain information on unsuccessful TOPs (this refers to incomplete expulsion of conception products), where medical methods are followed by surgical methods. Unsuccessful TOPs are not recorded on the Hospital Discharge Register either, and thus they could not be identified in this study. Moreover, information on use of cervical priming before surgical TOP could not be considered in this study. Furthermore, this study covered all the women with first birth including both spontaneously conceived and following assisted reproductive technologies (ART). We have not classified whether the pregnancy is spontaneously conceived or ART.

Socioeconomic status might be one of the potential confounders. However, it was not possible to control for that, as the data is incomplete in the register (Sub-studies I, II and III). It is difficult to define the socioeconomic status of a young woman such as that of a housewife or a student. Thus, smoking, which has been found as a good proxy for the socioeconomic status, is used in this study instead of the socioeconomic status (Laaksonen et al., 2005). The pre-existing health condition of mothers is likely to affect birth outcomes; however, it was not possible to adjust for the health condition of mothers because the data extracted for this study from the register did not contain such information (KC et al., 2018). Thus, there remains the possibility of unmeasured confounders which could not be controlled for.

In sub-study IV, socioeconomic status would have been great of interest. However, the information was incomplete in the register which has been already discussed above. The study period of the sub-study IV is quite long and there is possibility of change in time regarding repeat TOP. Therefore, a sub-analysis was performed for the most recent time period 2006-2015.

6.3 Comparison of major findings with other studies

This study found that the demographic and reproductive characteristics of first-time mothers with a history of TOP differed from those mothers without a history of TOP, which is consistent with the earlier studies (Klemetti et al., 2012; Raatikainen et al., 2006; Heikinheimo et al., 2008: Niinimäki et al., 2009) (Sub-studies I, II and III). The adjusted results of study I, showing no difference in risk of preterm birth and low birth weight among the mothers with surgical TOP compared to the

mothers with no TOP, do not concur with the earlier studies (Bhattacharya et al., 2012; Saccone et al., 2016). However, a few previous studies (Atrash & Hogue, 1990; Woolner et al., 2014; Zhou et al., 2000) support the findings of this study. In the Scottish study, gestational age at the time of TOP was not considered (Bhattacharya et al., 2012). Nonetheless, the finding of this study of borderline increased risk of SGA among mothers with surgical TOP compared to mothers with no TOP, corresponds to the finding of a previous meta-analysis (Saccone et al., 2016). As in one Chinese study (Chen et al., 2004), reduced risk of preterm birth among mothers with medical TOP compared to mothers with no history of TOP was observed in this study. Having had TOP reflects fertility, which might result in better birth outcomes in future pregnancy and also it is likely that medical TOP causes less trauma to the cervix resulting in better birth outcomes. However, the study was based on women's self-reported information and of small sample size (Chen et al., 2004).

The results of this study on increased risk of preterm birth and low birth weight after surgical TOP compared with medical TOP is consistent with previous studies (Bhattacharya et al., 2012; Lemmers et al., 2016; Liao et al., 2011; Shah et al., 2009). In contrast, few earlier studies found non-increased risk for preterm birth after surgical TOP than after medical TOP (Männistö et al., 2012; Virk et al., 2007). Contrary to some earlier studies (Chen et al., 2004; Männistö et al., 2012; Virk et al., 2007; Yimin et al., 2004), this study noted increased risk for low birth weight after surgical TOP than after medical TOP. Some of those studies were based on women's self-reported information which may cause bias by under-reporting (Chen et al., 2004; Liao et al., 2011; Virk et al., 2007).

In this study, women with multiple TOPs were associated with increased risk for extremely preterm birth, when women with no TOP were considered as a reference group, which is supported by the findings of earlier studies (Klemetti et al., 2012; Shah et al., 2009; Swingle et al., 2009). In this study (Study II), no difference was found in the risk for adverse birth outcomes when comparing multiple surgical and multiple medical TOPs, which is a similar finding as in two previous studies (Chen et al., 2004; Virk et al., 2007). However, another Chinese study found increased risks for preterm birth after multiple surgical TOPs compared with multiple medical TOPs (Liao et al., 2011). The study was based on self-reported information from women and under reporting could not be ruled out. Furthermore, it was difficult to assess the exact gestational age and method of TOP; and induced TOPs were not

differentiated from spontaneous TOPs. The findings of reduced risk of preterm birth after multiple TOP compared with no previous TOP was similar to the finding of the sub-study I. As discussed previously, less cervical trauma and infection caused by the medical procedure could be the possible biological mechanism for the better birth outcomes in future pregnancy. This study also looked for other outcomes such as SGA and perinatal death. The finding of increased risk of SGA after one surgical TOP compared with no TOP is in contrast with some other previous studies, that reported significant risk of SGA after TOP (Henriet & Kaminski, 2001; Raatikainen et al., 2006). The biological plausibility of the increased risk of SGA after TOP might be cervical insufficiency after surgical TOP, and post TOP complications such as uterine adhesions and infection. However, the biological mechanism is unclear and it is also possible that this is a chance finding.

Many studies explored the risk of adverse birth outcomes and TOP, but very few studies (Jackson et al., 2007; Kalish et al., 2002; Männistö et al., 2014; Schneider et al., 1996) have considered TOP performed in later gestation. The finding of this study (Sub-study III) on insignificant risk of preterm birth and low birth weight after early TOP compared with no TOP is similar to the finding of the previous study done in Scotland (Woolner et al., 2014). In contrast with some earlier studies (Jackson et al., 2007; Kalish et al., 2002; Männistö et al., 2014; Schneider et al., 1996), significantly increased risk of preterm birth and low birth weight were noted among women having had late TOP compared to women with no history of TOP in this study. However, few previous studies were based on surgical TOPs (Jackson et al., 2007; Kalish et al., 2002; Schneider et al., 1996b). In all these previous studies, no control group existed (Jackson et al., 2007; Schneider et al., 1996) and lack of adjustment for possible confounders was seen. In contrast with the findings of this study on increased risk of preterm birth and low birth weight after late TOP compared with early TOP, previous studies (Jackson et al., 2007; Woolner et al., 2014) did not find a difference in the risk of adverse birth outcomes among the women having had late and early TOP. A reduced risk for perinatal death was seen among late TOPs than early TOPs in this study. However, a German study did not find increased risk for perinatal after TOP (Reime et al., 2008). Sample size of the German study was small, and the under-reporting of previous TOP could not be ruled out. Moreover, perinatal death is a rare outcome and less studied in terms of TOP. In this study, the increased risk for SGA was found when comparing early or late TOP with no TOP, which differs from the result of a previous Italian study (Parazzini et al., 2007). However, the study had several limitations such as no

differentiation between legal and illegal TOPs, no consideration of method of TOP and possible selection bias in the control group.

Several previous studies showed the association between repeat TOP and various factors such as demographic factors, parity, contraception use and history of TOP (Heikinheimo et al., 2008; Li et al., 2021; Mccall et al., 2016; Mentula et al., 2010; Prager et al., 2007). The findings of this study on increased risk of repeat TOP among young women is similar to those of earlier studies (Heikinheimo et al., 2008; Mentula et al., 2010; Rose et al., 2015). However some studies reported that older age is associated with repeat TOP (Fisher et al., 2005; Justad-Berg et al., 2015; Li et al., 2021; Senso et al., 2022; Stone & Ingham, 2011). Consistent with previous studies (Justad-Berg et al., 2015; Mentula et al., 2010; Niinimäki et al., 2009), being single or unmarried and residing in urban areas were risk factors of repeat TOP. Young and single women might have financial problems in raising a child and having a child might interfere with their future opportunities. Also, women living in urban areas might seek TOP services more often because of easy access and availability of TOP services than those living in rural and semi-urban areas. The possible differences in educational level, income and traditional norms between the rural and urban women might influence the likelihood of repeat TOPs. As other studies, this study found being parous as a risk factor of repeat TOP (Heikinheimo et al., 2009; Li et al., 2021; Mccall et al., 2016; Stone & Ingham, 2011).

In this study medical TOP was found as a risk factor for repeat TOP considering the time period 1987-2015. However, including the recent time period after 2006, no difference was seen for repeat TOPs according to TOP method, which is consistent with earlier Finnish study (Niinimäki et al., 2009). The Finnish study considered the time-period after medical TOP was introduced, which could be one possible reason for increased risk among medical TOPs in this study considering the whole study period since 1987-2015. Additionally, other reasons could be the fact that medical TOP can be performed outside of a health care facility and women may feel the procedure to be less painful and more easily accessible. The study found a borderline increased risk for one repeat TOP after 12 gestational weeks and found no difference in risk for two or more repeat TOPs by gestational weeks at TOP. An earlier Finnish study found the second trimester TOP was associated with repeat TOPs and also with repeat TOPs during second trimester (Mentula et al., 2010).

The study finding that reliable method of contraception such as LARC, hormonal method and sterilization was associated with reduced risk of repeat TOP compared with reliable if used correctly (condom) or unreliable method, is supported by several earlier studies (Heikinheimo et al., 2008, 2009; Mccall et al., 2016; Rose et al., 2015). Previous studies reported that intrauterine contraception after TOP was highly effective in reducing the risk of repeat TOP (Niinimäki et al., 2009; Roberts et al., 2010). Moreover, previous studies reported reduction in TOP among women using LARC methods (Gyllenberg et al., 2018; Rose & Lawton, 2012). However, discontinuation in using LARC method might occur. A study reported discontinuation of using implants and copper intra device is higher than with a levonorgestrel-releasing intra-uterine system (Saloranta et al., 2020). Furthermore, initiation of any contraception immediately after TOP is likely to reduce the need for repeat TOP than not using any method (Heikinheimo et al., 2008; Li et al., 2021).

6.4 Public Health Implications of the results

Most of the women seek TOP at the outset of their reproductive life. Many women who have gone through TOP wish to get pregnant in their later life. Thus, these women should be informed about the possible consequences of TOP on future pregnancy and about the safer procedure, timing (gestational age) of TOP, multiple TOPs and the risk factors linked with multiple TOPs. Health education should be provided through different areas such as school health education and health education during outpatient and inpatient visits to doctors. Women seeking TOP should be properly counselled. Proper choice of contraceptives, easy access and low-cost or free contraception and immediate initiation of long-acting reversible contraceptive method would be helpful in reducing unwanted pregnancy and, ultimately, the need for TOP.

Many observational studies have been conducted using large datasets and tried their best to adjust for all possible confounders in establishing an association between TOP and future birth outcomes. Still, there is a need for further research, including complete information on important variables and that might be associated with poor birth outcomes and TOP that are lacking in this study, to find the safest technique and timing of the procedure in reducing adverse events in future pregnancy. It would be informative to study the possible adverse birth outcomes in more than one birth after TOP in further studies. Lack of information on cervical priming in this study

is one of our limitations because proper cervical priming would cause no harm to the cervix. The next research implications could be a study on the risk of adverse birth outcomes considering surgical TOP performed with cervical priming, which would provide more insights in drawing conclusions on the method of TOP.

7 CONCLUSIONS

This study suggests that surgical TOP is associated with higher risk of adverse birth outcomes in subsequent births. No differences were found in perinatal outcomes such as preterm birth, low birth weight, small for gestational age, and perinatal death after surgical TOP compared with the no history of TOP. However, increased risk for preterm birth and low birth weight was found after the surgical TOP than after medical TOP. Higher risk of adverse perinatal outcomes was found after repeat surgical TOP. Health education regarding the consequences of adverse birth events in subsequent birth should be provided to women and the use of proper contraception immediately after the TOP should be encouraged.

Increased risk of adverse birth outcomes is associated with TOP performed in later gestation than TOP performed in early gestation. This should be informed to women seeking TOP and services should be provided as early as possible, if required. Factors delaying TOP should be identified and avoided as much as possible.

Our study suggests the older age, married or cohabiting status and using reliable method of contraception were protective factors for repeat TOPs. However, being parous was found to be risk factor for repeat TOPs. Information regarding factors influencing repeat TOPs should be helpful for policy makers as well as women seeking TOP to reduce the need for repeat TOP.

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PUBLICATIONS

PUBLICATION 1

Perinatal outcomes after induced termination of pregnancy by methods: A nationwide register-based study of first births in Finland 1996-2013

Situ KC, Elina Hemminki, Mika Gissler, Suvi M. Virtanen, Reija Klemetti

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RESEARCH ARTICLE

Perinatal outcomes after induced termination of pregnancy by methods: A nationwide register-based study of first births in Finland 1996–2013

Situ KC[1]*, Elina Hemminki[2], Mika Gissler[3,4], Suvi M. Virtanen[1,5], Reija Klemetti[6]

1 School of Social Sciences, University of Tampere, Tampere, Finland, **2** Department of Health and Social Care Systems, National Institute for Health and Welfare, Helsinki, Finland, **3** Department of Information Services, National Institute for Health and Welfare, Helsinki, Finland, **4** Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden, **5** Department of Public Health Solutions, National Institute for Health and Welfare, Helsinki, Finland, **6** Department of Welfare, National Institute for Health and Welfare, Helsinki, Finland

* k.c.situ.x@student.uta.fi

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Abstract

Background

Women with previous terminations of pregnancy (TOPs) before their first birth have been associated with poorer perinatal outcomes. However, previous studies on the perinatal outcomes by the method in previous TOPs are inconsistent.

Objective

To examine the perinatal outcomes of the first-time mothers with singleton births, by the method of previous TOP (medical and surgical vs no TOP, and surgical vs medical).

Method

This is a nationwide register-based study including 419,879 first-time Finnish mothers with singleton birth during the time period 1996–2013. Mothers having their first birth were identified from the Medical Birth Register and linked to the Abortion Register by their identification numbers. Multinomial logistic regression analysis was performed to examine the risk for preterm birth, low birth weight, small for gestational age and perinatal death by the method in previous TOPs.

Results

Among the first-time mothers, 87.0% had no history of TOPs, 3.2% had a history of medical TOP(s), 9.2% had a history of surgical TOP(s) and 0.6% had a history of both (medical and surgical) TOP(s). No significant differences in perinatal outcomes were found among the women with surgical TOPs, compared to the women with no TOPs. In unadjusted analysis, increased odds for preterm birth and low birth weight were found when comparing women having previous surgical TOPs with medical TOPs. Even after the adjustment of potential

https://www.thl.fi/en/web/thlfi-en/statistics/information-for-researchers and email address of secretary, sampo.viiri@thl.fi.

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confounders, odds for preterm birth < 37 weeks (OR = 1.19, 95% CI = 1.04–1.36) and low birth weight < 2500 g (OR = 1.16, 95% CI = 1.00–1.35) remained significant. After restricting data to the single TOP, the results were similar; OR for both preterm birth and low birth weight was 1.18 (95% CIs = 1.02–1.36 and 1.01–1.38).

Conclusion

Perinatal outcomes did not differ among the mothers with surgical TOPs compared to the mothers with no TOPs, while the outcomes were poorer after surgical TOP(s) than after medical TOP(s).

Introduction

In Europe, termination of pregnancies (subsequently TOPs) are common, and in Western European countries most TOPs are performed before the first birth [1]. Finland has low rate of TOP, and in 2014 the rate was 8.5 per 1,000 women aged 15–49 years old. The highest rate was among women aged 20–24 years old (16.8 per 1,000 women), which is well below the mean age (28.6 years old) of a woman's first childbirth [2].

A termination of pregnancy can be performed by surgical (dilatation and uterine evacuation) or medical (antiprogestin mifepristone and misoprostol) methods. In Europe, medical TOPs began in France in 1998 [3]. Mifepristone received authorization in Finland in 2000. Since then, there have been increased use of medical termination of pregnancy and it was nearly 90% in 2014 [2].

Whether or not an induced termination of pregnancy prior to the first birth adversely influences the outcome of that birth has been previously debated [4–8]. There are evidences of an increased risk of preterm birth with many TOPs prior to the first birth [5–8], but these results refer to the time period when most TOPs were surgical. However, some studies did not found an association between previous TOPs and preterm birth/ low birth weight [4,9–11].

Few studies have considered the method of TOPs, with regard to the outcomes in subsequent birth [9,12–18]. Some studies have reported a higher risk of preterm birth and low birth weight after surgical TOPs, when compared to medical TOPs [15,17], but others have found no increased risk in outcomes between these methods [14,16,18]. Although no other studies have taken into account the number of TOPs when comparing these methods, a study from China [15] has reported an increased risk for preterm birth among those mothers with repeated surgical TOPs, compared to those mothers with repeated medical TOPs.

A previous study from Finland found an increased risk for poorer perinatal outcomes after many TOPs, however data was too scant to study the outcomes by the method of abortion [8]. Thus the purpose of this study was to examine the perinatal outcomes of first-time mothers with singleton birth by the method of TOP: medical and surgical vs no TOP, and surgical vs. medical TOP(s), while adjusting for confounding factors. Additionally, comparisons were made between those mothers with only one previous TOP in their reproductive histories.

Methods

The study was approved by the ethical committee of National Institute for Health and Welfare (THL). A positive statement from THL ethics committee (22.10.2009), a positive statement with regard to the amendment of the data, and a permission to use the data were received

from THL (25.10.2014). The information used in this study were anonymized prior the analysis.

In this population-based cohort study, we used the nationwide Medical Birth Register (MBR) and Abortion Register (AR), which were maintained by the National Institute for Health and Welfare (THL). All the mothers having had their first birth during the time period ranging from 1996 to 2013 were identified from the MBR, and these mothers were linked to the AR to determine the TOPs (1983–2013) they had prior to their first birth. The MBR was started in 1987, and it contains information about each mother's background characteristics, care during pregnancy and delivery, and newborn care up to 7 days of age [2]. The AR has been functional since 1950, and computerized data are available since 1983 [19]. The register contains information on a woman's background, gestational age, indication for TOPs, dates, procedures and complications occurring during the process [19]. Overall, the information in both registers is relatively complete, and the data quality is high [19–20].

For this study, the mothers were divided into four study groups by their TOP histories and methods: no prior TOP, medical TOPs only, surgical TOPs only and both types of TOPs. The medical TOPs included TOPs performed using mifepristone alone, or in combination with misoprostol. Surgical TOPs included TOPs performed using either dilatation and curettage or vacuum aspiration. Mothers who had undergone multiple TOPs using both medical and surgical methods were included in both types of TOPs. Only the mothers with successful TOPs were included. The proportion of failed TOPs is very low; 0.4% in 2009–2015 according to the Abortion Register.

The outcome measures, gestational age at birth, birth weight, small for gestational age and perinatal death were retrieved from the MBR. The gestational age at birth in the MBR is the clinicians' best estimate at birth, based on ultrasound examination(s) and the date of last menstruation. The birth was defined as preterm if the gestational age at birth was less than 37 weeks, very preterm if the gestational age at birth was less than 32 weeks and extremely preterm if the gestational age was less than 28 weeks. Birth weights of less than 2,500 grams and 1,500 grams were defined as low birth weight and very low birth weight, respectively. Small for gestational age (SGA) was defined according to sex-specific Finnish standards for newborn infants between 24 and 43 gestation weeks [21]. Perinatal deaths referred to stillbirths from 22 weeks of gestation and early neonatal deaths until the end of the first week after birth.

The background characteristics of women were received from the MBR and they refer to the time of the birth of the baby. The urbanity of the maternal municipality of residence was categorized according to Statistics Finland, and the categories were further grouped into urban, semi-urban, rural and abroad. In the MBR, marital status of mothers was categorized into seven categories; married and living together with spouse, registered partnership, married and living separated from spouse, never married, divorced, widowed and unknown. These were further categorized into three groups; married/cohabiting, unmarried/single and unknown. In this study, we treated all variables as categorical variables. Information concerning socioeconomic status of the mothers was incomplete. So, maternal smoking and urbanity of municipality were used to explain the socioeconomic status of mothers.

The statistical software, SPSS 23, was used for the analysis. Cross tabulations based on the study groups were calculated and chi-square test were used to study statistical significance. The level of statistical significance was set at $p<0.05$. Those mothers with previous surgical TOPs and those with previous medical TOPs were separately compared to women with no previous TOP, adjusting for differences in their background characteristics using a multivariate logistic regression (odds ratio and 95% confidence interval). The potential confounders were selected on the basis of the previous literature on the maternal risk factors of birth outcomes, and their availability and quality in the registers. Mothers with previous TOPs (surgical

or medical) were compared to those without previous TOP, after adjusting for the maternal age, marital status, urbanity of the municipality of residence, history of smoking during pregnancy and the year of childbirth.

Mothers with previous surgical TOPs were compared to those with previous medical TOPs, after adjusting for the maternal age, marital status, urbanity of the municipality of residence, history of smoking during pregnancy and the year of childbirth. In the second model, additional adjustments (number of previous TOPs, gestational age at TOP and year of last TOP) were added. Since the number of women having had both medical and surgical TOPs was small when compared to the other groups, these mothers were excluded from the regression analysis. Lastly, a sub-analysis for those mothers having had only one previous surgical or medical TOP was conducted, after adjusting for the same confounders as above.

Results

A total of 419,879 first-time mothers having had singleton birth from 1996–2013 were identified from the MBR. According to the AR, 365,356 (87.0%) of the mothers had no history of TOP, 13,450 (3.2%) had histories of medical TOP(s), 38,659 (9.2%) had histories of surgical TOP(s) and 2,414 (0.6%) had histories of both medical and surgical TOP(s). The background characteristics differed with regard to several aspects between these subgroups (Table 1). The mothers with histories of previous TOPs were more often younger, single, urban residents and smokers than the mothers without previous TOP. When compared to the mothers with previous medical TOPs, the mothers with previous surgical TOPs had more repeated TOPs, had their last TOP in earlier years, and the time difference between their first birth and last TOP was longer (Table 2).

When compared to those mothers with no previous TOP, the perinatal outcomes were poorer among those mothers with previous surgical or both types of TOPs, but not among the mothers with previous medical TOPs only (Table 3). The incidence of preterm birth was lower among the mothers with previous medical TOPs, when compared to those mothers without previous TOPs.

The unadjusted logistic regression analysis showed increased risk for all types of preterm birth and low birth weight after surgical TOPs and decreased risk for all studied perinatal outcomes after medical TOPs, when compared to the mothers without previous TOP (Table 4). Compared to the mothers with previous medical TOPs, the mothers with previous surgical TOPs had increased risk for all studied outcomes, with the exception of SGA and perinatal death.

After adjusting for the sociodemographic factors, the mothers with previous medical TOPs had decreased risk for preterm birth and low birth weight when compared to the mothers with no previous TOPs (Table 4). The increased risk for adverse outcomes when comparing the mothers with surgical TOPs to the mothers with no TOPs, did not remain significant, after controlling for background characteristics. However, mothers with surgical TOPs had marginally increased risk for SGA compared to the mothers with no TOPs.

The mothers with previous surgical TOPs had higher risk for preterm birth and newborn with low birth weight than those mothers with previous medical TOPs (Table 4). After an additional adjustment for the number of previous TOPs, the gestational age at the time of TOP, year of the last TOP, risk for preterm birth (<37 weeks) and risk for newborn with low birth weight remained significant (Table 4).

After restricting the analysis to those mothers having had only one previous TOP, and adjusting for confounders, the results did not change: the mothers having had only one

Table 1. Background characteristics of Finnish first-time mothers in 1996–2013 by previous TOPs and methods.

Characteristics	No prior TOP (n = 365356)	Medical TOP (n = 13450)	Surgical TOP (n = 38659)	Both (n = 2414)	Total (n = 419879)	P-value*
	%	%	%	%	%	
Maternal age						
Mean (SD)	27.4 (5.2)	26.1 (5.3)	28.2 (5.5)	27.4 (5.5)	27.4 (5.2)	<0.0001
≤19	5.8	8.3	4.6	3.6	5.8	
20–24	24.5	35.7	22.6	28.1	24.7	
25–29	36.9	31.4	32.7	32.6	36.3	
30–34	23.6	17.2	26.3	23.2	23.7	
35–39	7.7	5.9	11.2	9.6	7.9	
≥40	1.5	1.4	2.6	2.9	1.6	
Marital status						
Married/cohabiting	86.0	78.6	77.5	74.4	84.9	<0.0001
Unmarried/Single	12.6	20.8	20.3	25.1	13.7	
Unknown	1.4	0.6	2.2	0.6	1.4	
Type of residence						
Urban	71.1	73.3	73.3	76.0	71.4	<0.0001
Semi-urban	14.2	14.1	14.1	12.2	14.1	
Rural	14.1	11.9	13.1	11.2	13.9	
Abroad	0.6	0.7	0.4	0.5	0.6	
Smoking status						
No smoking	82.7	63.5	67.6	54.8	80.5	<0.0001
Stopped smoking in third trimester	4.8	11.9	6.3	11.6	5.2	
Smoked after first trimester	10.5	22.6	23.8	31.5	12.3	
Birth year of child						
1996–2000	26.7	3.9	36.1	7.9	26.7	<0.0001
2001–2005	27.2	12.4	33.2	18.5	27.2	
2006–2010	29.1	43.9	22.9	45.3	29.1	
2011–2013	17.0	39.8	7.9	28.3	16.9	

*P-value from chi square test and statistical significance at the level of 0.05

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previous surgical TOP had increased risks for preterm birth and low birth weight when compared to the mothers with only one previous medical TOP (Table 4).

Discussion

The first-time mothers with previous TOP were much younger, single and more often smokers than the mothers without previous TOP. In addition, the mothers with previous medical TOPs had a reduced risk for preterm birth and low birth weight when compared with the mothers with no previous TOP. All the poor outcomes measured, with the exception of small for gestational age and perinatal deaths, were more common among the mothers with previous surgical TOPs than among the mothers with previous medical TOPs. This was also true among those mothers who had gone through only one TOP before their first birth.

Our nationwide study covered all the first-time mothers having had singleton births during the time period ranging from 1996 to 2013, and all of the TOPs performed in Finland during the time period ranging from 1983 to 2013. Because our data did not include TOPs before 1983, some women might have been classified wrongly into the "no TOP group". However, we assume that there are only few such cases and this will thus not affect our results. The quality

Table 2. History of TOPs of Finnish first-time mothers in 1996–2013 by their methods.

History of TOPs	Medical TOP (n = 13450)	Surgical TOP (n = 38659)	Both TOP (n = 2414)	Total (n = 54523)	P-value*
	%	%	%	%	
Number of TOPs					
1	90.6	87.5	0.0	84.4	<0.0001
2	8.1	10.5	71.3	12.6	
≥3	1.3	2.0	28.7	3.0	
Gestational age at TOP					
<12 weeks	77.0	90.4	61.4	85.8	<0.0001
≥12 weeks	23.0	9.6	38.6	14.2	
Year of last TOP					
1987–1994	3.3	33.1	4.9	23.9	<0.0001
1995–1998	3.3	29.4	7.2	21.4	
1999–2003	25.0	28.2	28.9	27.4	
2004–2013	68.3	9.2	59.1	27.3	
Difference between first birth and last TOP					
5–38 months	50.2	24.6	53.4	32.8	<0.0001
39–81 months	35.4	33.0	34.0	33.7	
82–310 months	14.4	42.4	12.6	33.5	

*P-value from chi square test and statistical significance at the level of 0.05

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of the data from the THL and AR is considered to be very high and reliable [19,20], and earlier studies have compared the information in the medical records with the AR and found that 95% of the information matched and 99% data coverage [19,21]. Our large data set enabled us to study the outcomes in different subgroups, based on the method of terminating pregnancy. Even though we were able to study the outcomes by the method we were not able to separate different medical (mifepristone/misoprostol) or surgical methods (dilatation, curettage or vacuum aspiration) because the register do not contain as detailed information. Furthermore, this is an observational study and it cannot provide evidences for causality.

Overall, our findings that the demographic and reproductive profiles of first-time mothers with histories of previous TOPs differed from those of first-time mothers without histories of previous TOPs are in line with previous studies [8,11,22,23]. In the multivariate logistic regression analysis, we were able to adjust for several background variables; however, we could not adjust for the socioeconomic position of the mothers due to incomplete data (data not shown).

Table 3. Incidence of perinatal outcomes among the Finnish first-time mothers in 1996–2013 by previous TOPs and methods.

Perinatal outcomes	No prior TOP (n = 365356)		Medical TOP (n = 13450)		Surgical TOP (n = 38659)		Both (n = 2414)		Total (n = 419879)	
	n	/1000	n	/1000	n	/1000	n	/1000	n	/1000
Extremely preterm birth <28 weeks	1122	3	38	3	154	4	11	5	1325	3
Very preterm birth <32 weeks	1843	5	57	4	232	6	10	4	2142	5
Preterm birth <37 weeks	17041	47	515	38	1882	49	105	44	19542	47
Very low birth weight <1500 grams	2805	8	90	7	341	9	20	8	3256	8
Low birth weight <2500 grams	12439	34	417	31	1447	37	88	36	14391	34
Small for gestational age	17897	49	687	51	2047	53	136	56	20767	49
Perinatal death	1622	4	58	4	206	5	13	5	1899	5

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Table 4. Crude and adjusted ORs and 95% confidence intervals for perinatal outcomes of Finnish first-time mothers according to the method of TOP.

Perinatal outcomes	Odds Ratios and 95% Confidence Interval							
	Medical vs no TOP[1]		Surgical vs no TOP[1]		Surgical vs medical TOP[2]		Surgical vs medical TOP, only one TOP[3]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Extremely preterm birth <28 weeks								
Crude Model	0.91	0.66–1.26	1.30	1.10–1.54	1.43	0.99–2.04	1.32	0.91–1.92
Adjusted Model I	0.94	0.68–1.30	1.16	0.98–1.38	1.20	0.79–1.81	1.12	0.73–1.73
Adjusted Model II					1.43	0.90–2.30	1.39	0.84–2.30
Very preterm birth <32 weeks								
Crude Model	0.83	0.64–1.08	1.19	1.04–1.37	1.44	1.07–1.92	1.33	0.98–1.80
Adjusted Model I	0.88	0.67–1.15	1.03	0.89–1.18	1.23	0.87–1.71	1.13	0.80–1.61
Adjusted Model II					1.24	0.85–1.81	1.23	0.83–1.84
Preterm births <37 weeks								
Crude Model	0.81	0.74–0.89	1.05	1.00–1.10	1.29	1.17–1.43	1.26	1.13–1.40
Adjusted Model I	0.83	0.76–0.91	1.00	0.95–1.05	1.16	1.03–1.30	1.15	1.02–1.29
Adjusted Model II					1.19	1.04–1.36	1.18	1.02–1.36
Very low birth weight <1500 grams								
Crude Model	0.87	0.70–1.07	1.15	1.03–1.29	1.33	1.05–1.68	1.25	0.98–1.60
Adjusted Model I	0.88	0.71–1.10	1.00	0.89–1.12	1.16	0.89–1.52	1.11	0.84–1.47
Adjusted Model II					1.27	0.93–1.73	1.27	0.91–1.76
Low birth weight <2500 grams								
Crude Model	0.91	0.82–1.00	1.10	1.04–1.17	1.22	1.09–1.36	1.21	1.08–1.36
Adjusted Model I	0.86	0.78–0.95	0.98	0.93–1.04	1.16	1.02–1.32	1.16	1.01–1.32
Adjusted Model II					1.16	1.00–1.35	1.18	1.01–1.38
Small for gestational age								
Crude Model	0.96	0.88–1.03	0.92	0.88–0.97	0.96	0.88–1.05	0.96	0.88–1.05
Adjusted Model I	1.05	0.97–1.14	1.07	1.02–1.12	0.99	0.89–1.10	0.99	0.89–1.10
Adjusted Model II					1.00	0.89–1.13	1.01	0.89–1.14
Perinatal death								
Crude Model	1.03	0.79–1.34	0.83	0.72–0.96	0.81	0.60–1.08	0.81	0.60–1.08
Adjusted Model I	0.97	0.74–1.27	0.98	0.85–1.14	1.13	0.80–1.60	1.13	0.80–1.60
Adjusted Model II					1.00	0.67–1.48	1.00	0.67–1.48

Adjusted Model I- adjusted for socio demographic factors; maternal age, marital status of mothers, area of residence, smoking status and year of child birth

Adjusted Model II- adjusted for number of previous TOPs, gestational age at TOP and the year of last TOP

[1] No TOP group is used as reference group

[2] Medical group is used as reference group

[3] Medical group is used as reference group and includes mothers with only one medical and one surgical TOP

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In Finland, smoking has been found to be a good proxy for the socioeconomic position [24]; therefore, we used urbanity of municipality and mother's smoking instead.

Previously, it has been reported that undergoing several TOPs before a woman's first birth correlated with poorer perinatal outcomes in subsequent births [5–8]. However, we compared the mothers with histories of surgical and medical TOPs, but adjusted for the number of previous TOPs. Moreover, we conducted a subgroup analysis of those having had only one surgical or medical TOP. We also adjusted for the gestational age at the time of TOP and the year of the last TOP, which has not been done in previous studies [12,15,17,25].

There are few studies examining the long-term consequences of medical TOPs [14,16]. However, our finding of a reduced risk of preterm births among the mothers with previous medical TOPs, when compared to the mothers with no previous TOP, is consistent with a previous study from China [13]. In addition, some other studies [14,15,17] indirectly support our finding of no increased risk for preterm births among the mothers with history of medical TOPs. Having had a TOP reflects fertility, and this may explain the better outcomes among those mothers having had medical TOPs compared to the mothers without history of TOPs. Poorer outcomes after surgical TOPs might be due to the reason that the medical TOPs cause less physical trauma to the cervix and the less endometrial damage than the surgical TOPs [6,13,26,27].

As in some prior studies, our unadjusted results showed an increased risk for preterm births among those mothers with surgical TOPs, when compared with those mothers having had no prior TOPs [15,17,18,25]. However, in our study, the significance was lost after adjusting for the sociodemographic factors.

Similar to some previous studies [9,15,17,25], we found a higher risk for preterm births among the mothers with previous surgical TOPs, when compared to the mothers with previous medical TOPs. Medical TOPs may cause less harm to the uterus than surgical TOPs, which can result in better birth outcomes later [13,27]. A recent review and meta-analysis from 21 studies also supports our findings with regard to the association between preterm births and surgical TOPs [28]. In contrast, some previous studies have not found an increased risk for preterm births in subsequent births among mothers with previous surgical TOPs, when compared to mothers with previous medical TOPs [11,14,29]. However, some of those studies did not control for potential confounders, and some were based on self-reported TOPs, which may introduce recall bias [13,14].

Contrary to some of the previous research, our study reported an increased risk for low-birth weight among the mothers with previous surgical TOPs, when compared to the mothers with previous medical TOPs [12–14,16]. However, few studies found a positive association between surgical TOPs and the risk of low birth weight [4,9], which might support our findings.

Conclusion

Perinatal outcomes did not differ among the mothers with surgical TOPs compared to the mothers with no TOPs, while the outcomes were poorer after surgical TOP(s) than after medical TOP(s). It is important to study the effects of the different methods used for terminating pregnancy to determine the safest method. This could be of importance for healthcare professionals in terms of clinical decision making and counselling women seeking termination of pregnancy, with respect to the method used for termination.

Author Contributions

Conceptualization: Situ KC, Elina Hemminki, Mika Gissler, Reija Klemetti.

Data curation: Mika Gissler.

Formal analysis: Situ KC.

Funding acquisition: Situ KC, Reija Klemetti.

Investigation: Situ KC, Reija Klemetti.

Methodology: Situ KC, Reija Klemetti.

Project administration: Situ KC, Mika Gissler, Reija Klemetti.

Resources: Situ KC, Suvi M. Virtanen, Reija Klemetti.

Software: Situ KC.

Supervision: Suvi M. Virtanen, Reija Klemetti.

Validation: Situ KC.

Visualization: Situ KC, Elina Hemminki, Mika Gissler, Reija Klemetti.

Writing – original draft: Situ KC.

Writing – review & editing: Situ KC, Elina Hemminki, Mika Gissler, Suvi M. Virtanen, Reija Klemetti.

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PUBLICATION 2

Risks of Adverse Perinatal Outcomes after Repeat Terminations of Pregnancy by their Methods: a Nationwide Register-based Cohort Study in Finland 1996–2013

Situ KC, Mika Gissler, Suvi M. Virtanen, Reija Klemetti

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Risks of Adverse Perinatal Outcomes after Repeat Terminations of Pregnancy by their Methods: a Nationwide Register-based Cohort Study in Finland 1996–2013

S. KC,[a] M. Gissler,[b,c] S. M. Virtanen,[a,d] R. Klemetti[e]

[a]Faculty of Social Sciences, University of Tampere, Tampere, Finland

[b]Department of Information Services, National Institute for Health and Welfare, Helsinki, Finland

[c]Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden

[d]Department of Public Health Solutions, National Institute for Health and Welfare, Helsinki, Finland

[e]Department of Welfare, National Institute for Health and Welfare, Helsinki, Finland

Abstract

Background: Repeat terminations of pregnancy (TOPs) are associated with an increased risk of adverse outcomes in the subsequent birth. The perinatal outcomes after repeat TOPs by their methods have not yet been properly studied. This study aimed to examine perinatal outcomes in subsequent pregnancy among the women with a singleton birth and a history of TOPs.

Methods: All the first-time mothers (n = 419 879) with a singleton birth during 1996–2013 in Finland were identified from the Medical Birth Register and linked to the Abortion Register. Adjusted multivariable logistic regression analysis was used to estimate risks of adverse perinatal outcomes.

Results: The increased incidence of adverse perinatal outcomes was found with increasing number of surgical TOPs. After adjusting for confounders, the women with one surgical TOP had slightly increased but significant odds of 1.07 (95% CI 1.02, 1.13) for being small for gestational age compared with the women having no TOP. A significantly high risk for extremely preterm birth (OR 1.51, 95% CI 1.03, 2.23) was found among the women having had repeat surgical TOPs when compared to the women with no TOP. Non-significant risks were found for adverse perinatal outcomes after women's repeat surgical TOPs than repeat medical TOPs.

Conclusion: Information regarding the consequences of repeat induced TOPs will be significant in sexual health education as well as counselling women after first termination.

Repeat termination of pregnancy (TOP) is an important worldwide public health concern. The rate of repeat TOP is high such as 37% in England and Wales, 50% in the United States, and 43% in Sweden.[1–3] In Finland, however, the overall number of TOPs has decreased during the recent years,[4] still the number of repeat TOPs is high as 37% of women who are seeking TOP had gone through at least one previous TOP.[4]

Many studies have examined the association between history of TOPs and perinatal outcomes.[5–13] It has been evidenced that a single TOP is not a risk factor for preterm birth,[12,13] however, repeat TOPs are associated with increased perinatal risks.[5–11] The previous studies did not consider the methods of TOP in relation to adverse perinatal outcomes; however, most of the TOPs were surgical.

The surgical methods of TOPs (dilatation and curettage) have been gradually replaced by medical methods (mifepristone and misoprostol). Medical TOPs were first started in Finland in 2000, and by 2014, the rate of medically induced TOP reached 90%.[4]

A high risk of preterm birth and low birthweight after surgical TOPs compared to the medical TOPs has been reported in some studies,[14,15] while few other studies have found no difference in the outcomes between the two methods.[16–18] Most of the studies were limited by a small sample size and were based on self-reported information on TOPs.[5,7,19]

Correspondence:
Situ KC, Faculty of Social Sciences, University of Tampere, FI-33014 Tampere, Finland.
E-mails: situkc11@gmail.com, k.c.situ.x@student.uta.fi

Moreover, some studies were not able to control for the history of TOPs such as year of TOP, gestational age at TOP, and the method.[5,7,19,20]

A study from China explored the risk in preterm births after repeat TOPs and reported no association between repeat medical TOPs and a higher risk of preterm birth compared to those without previous TOP.[14] However, the study was based on women's self-report. Our previous study (unpublished data, paper under review) found a higher risk for preterm birth and low birthweight infant after surgical TOP compared to medical one. In the earlier study, we did not examine the perinatal outcomes by the number and the method of the TOPs. Thus, the previous studies on long-term consequences of repeat TOPs by their methods on subsequent birth are limited and need further exploration.

The purpose of this study was to examine the risk of preterm birth, perinatal death, and small for gestational age among the first-time Finnish mothers with a singleton birth after their repeat terminations of pregnancy by the method of TOPs.

Methods

In this register-based study, the Medical Birth Register (MBR) and the Abortion Register (AR) maintained by the National Institute for Health and Welfare (THL) were used. All the first-time mothers with singleton birth during 1996–2013 were identified from the MBR and linked to the data of the AR to trace TOPs during the period 1983–2013. The MBR was considered from 1987 and the information on mother's background, care during pregnancy, and delivery, as well as newborn care up to 1 week, was included.[4] The AR has been operational since 1950, and computerized data are available since 1983.[21] The register covers the information on women's background, gestational week of TOP, reasons for TOPs, dates, procedures, numbers, and complications occurring during the process.[21] The data from both registers are reliable and of high quality.[21,22]

In this study, we categorized women who were first-time mothers with the singleton birth according to the number of prior TOPs and divided into four categories: no prior TOP, one TOP, two TOPs, and more than two TOPs. These women were further categorized on the basis of the methods used in prior TOPs: no prior TOP, one TOP (either medical or surgical), two TOPs (either of two medical, two surgical, or one medical and one surgical) and more than two (either of more than two medical, more than two surgical, and more than two both types of TOPs, i.e. medical and surgical). Medical TOPs included the women whose TOPs were performed medically using mifepristone alone or in a combination of mifepristone and misoprostol. Surgical TOP included the women whose TOPs were performed using dilatation and curettage or vacuum aspiration. The both groups included women who had gone through TOPs using both medical and surgical methods.

We derived the data on outcome measures, gestational age at birth (based on last menstruation and ultrasonography in early pregnancy), perinatal death and small for gestational age (SGA), from the MBR. The preterm birth was defined as the birth before a 37-week gestation, very preterm birth before a 32-week gestation, and extremely preterm birth before a 28-week gestation. Perinatal deaths referred to the deaths from 22 weeks of gestation until the end of the first week after birth. SGA was defined according to sex-specific Finnish standards for newborn infants between 24 and 43 gestation weeks.[23] The proportion of missing cases were low: 0.2% for gestational age at birth and 0.03% for birthweight, and, therefore we did not apply any methods for handling missing values.

The statistical analysis was done using STATA version 14. Chi-square test was used to determine the differences between subgroups. The level of statistical significance was set at $p < 0.05$.

In the first analysis, women with no history of TOP were compared to the subgroups of women with previous TOP(s), adjusting for the differences in background characteristics using logistic regression (odds ratio and 95% confidence intervals). The potential confounders such as maternal characteristics (age, residence, marital status, smoking, and birth year of the child), gestational age at TOP and the year of last TOP were selected on the basis of previous studies on maternal risk factors for perinatal outcomes and their availability and quality in the health care registers. The number of women assigned to both group was small, so the women belonging to the groups were excluded while comparing to women with no prior TOP.

In the second analysis, subgroup analysis was done to compare the surgical and the both group with the medical group. This study was particularly focused on repeat TOPs thus, the comparison between single medical and surgical induced TOP was excluded for further analysis. Due to the low number of repeat

TOPs (medical, surgical, and the group with both), we combined all the categories with more than one TOP into a single category (at least two TOPs) for regression analysis. The women who had at least two medical TOPs were compared to the women who had at least two surgical TOPs and those having both types of TOP, i.e. at least one medical and one surgical TOP. Further, the women having a single medical or surgical TOP were compared to those having at least two medical or surgical TOPs. Adjustments were made for women's background characteristics such as maternal age, marital status, urbanity of residence municipality, smoking during pregnancy, and year of childbirth and the gestational age at the TOP along with the year of last TOP.

An approval from the ethics committee of National Institute for Health and welfare (THL) was received on 22.10.2009 and the permission to use the confidential register data in this study was granted from THL on 22.10.2014.

Results

Of all the first-time Finnish mothers with singleton birth (n = 419 879) during 1996–2013, 87% had no previous TOP, 11% had one TOP, 1.6% had two TOPs, and 0.4% had more than two TOPs. Most of the TOPs were performed during the first trimester (87%) and only few (13%) were made during the second trimester of pregnancy. We found significant differences between the subgroups of women with respect to background characteristics (Table 1). Women with the history of TOPs were more often younger, urban residents, single and smokers than the women with no history of TOP.

The incidence of an extremely preterm birth, very preterm birth, preterm birth, perinatal mortality, and SGA after surgical TOPs increased with the additional number of TOPs (Figure 1). After medical TOPs, however, an increased incidence was found only for SGA (Figure 1).

In the univariate analysis, compared to the women with no TOP, those having a history of one surgical TOP had significantly higher risk of extremely preterm birth and very preterm birth (Table 2). The women with at least two surgical TOPs had significantly higher risk for extremely preterm birth and very preterm birth. After adjusting for maternal characteristics (age, urbanity of municipal residence, marital status, smoking status, and the year of childbirth), the women with a single surgical TOP had 1.1-fold higher risk for SGA infants and women with the history of at least two surgical TOP had 1.5-fold higher risk for extremely preterm birth compared to the women who had no TOP. Compared to the women with no TOP, the women with one previous medical TOP had a reduced risk for preterm birth and the women with at least two medical TOPs had a low risk for preterm birth.

In the unadjusted analysis, while comparing the outcomes after repeat surgical TOPs and both the types of TOPs to those after repeat medical TOPs, high risks for several adverse perinatal outcomes were found, but the risks were not statistically significant and decreased after adjusting for maternal characteristics, gestational age at TOP, and the year of last TOP (Table 3). The risks for adverse perinatal outcomes did not increase when comparing the women with one medical induced TOP to women with at least two medical TOPs (Table 3).

Comment

Main findings

A slightly elevated but statistically significant risk for SGA infants after one previous surgical TOP and a highly significant risk for extremely preterm birth after repeat (at least two) surgical TOPs were found, compared to the women with no previous TOPs. Several increased but non-significant risks were found for adverse perinatal outcomes after repeat surgical TOPs compared to repeat medical TOPs. No increased risk for any adverse perinatal outcomes was found after repeat medical TOPs compared to a single medical TOP.

Strengths of the study

Our study is the largest one which included all the first-time Finnish mothers with singleton birth within a period of 18 years and all the TOPs performed since 1983. We used the national register data from THL, which have been confirmed to be reliable and of high quality.[21,22] The information contained in the Finnish Abortion Registry was valid and 95% of the information corresponded with the medical records.[21,24] Our previous study (unpublished data, still under review) using the same dataset explored the risk for adverse perinatal outcomes by the different methods used in prior induced TOPs, but in that study, we did not

Table 1. Demographic characteristics of first-time Finnish mothers by number and methods of TOP in Finland during 1983–2013

Demographic characteristics	No TOP (%) (n = 365356)	One induced TOP		Two induced TOPs			At least two induced TOPs			Total (%) (n = 419879)
		Medical (%) (n = 12183)	Surgical (%) (n = 33840)	Two medical (%) (n = 1092)	Two surgical (%) (n = 4048)	Medical and surgical (%) (n = 1721)	Medical only (%) (n = 175)	Surgical only (%) (n = 771)	Both medical and surgical (%) (n = 693)	
Maternal age										
Mean (SD)	27.35 (5.18)	26.13(5.33)	28.11(5.51)	25.13 (4.70)	28.89 (5.56)	27.47 (5.56)	25.62 (4.44)	29.69 (5.31)	28.46 (5.24)	27.39 (5.23)
≤19	5.81	8.53	4.87	6.50	3.14	4.42	5.71	1.17	1.73	5.77
20–24	24.52	34.70	23.04	45.97	20.43	29.63	40.57	16.08	24.24	24.72
25–29	36.87	31.37	32.72	31.78	31.92	31.44	33.14	34.24	35.50	36.29
30–34	23.65	17.81	26.03	10.44	27.84	22.60	17.14	30.35	24.53	23.68
35–39	7.66	6.05	10.87	4.58	13.49	9.01	3.43	13.62	10.97	7.94
≥40	1.49	1.53	2.46	0.73	3.19	2.91	0.00	4.54	3.03	1.60
Residence										
Urban	71.09	73.14	72.74	73.72	76.63	75.36	81.71	76.91	77.63	71.38
Semi-urban	14.23	14.23	13.56	13.28	11.68	12.32	12.00	11.02	11.98	14.13
Rural	14.07	11.93	13.35	12.73	11.34	11.68	5.71	11.54	10.10	13.90
Abroad	0.61	0.70	0.35	0.27	0.35	0.64	0.57	0.52	0.29	0.59
Marital status										
Married/ cohabiting	86.01	79.02	78.23	74.45	73.25	74.49	72.57	68.35	74.03	84.93
Unmarried/single	12.62	20.31	19.59	25.27	24.16	24.93	26.86	28.92	25.40	13.65
Others	1.37	0.67	2.18	0.27	2.59	0.58	0.57	2.72	0.58	1.42
Smoking status of mothers										
No smoking	82.67	64.75	69.16	52.01	57.83	56.94	50.29	51.75	49.64	80.52
Quitted smoking	4.83	11.55	6.29	14.84	6.55	10.98	17.14	7.91	13.13	5.23
Smoked through pregnancy	10.52	21.75	22.37	31.23	32.66	30.27	29.71	38.13	34.63	12.25
Others	1.97	1.95	2.19	1.92	2.96	1.80	2.86	2.20	2.60	2.00
Birth year of child										
1996–2000	21.43	3.43	29.24	0.55	27.96	6.74	0.00	24.77	4.04	21.45
2000–2004	26.84	9.44	33.66	2.93	36.46	14.76	0.57	40.73	11.11	26.85
2005–2008	22.83	27.21	21.31	20.79	21.25	33.29	13.71	22.70	32.32	22.87
2009–2013	28.90	59.92	15.79	75.73	14.33	45.21	85.71	11.80	52.53	28.82

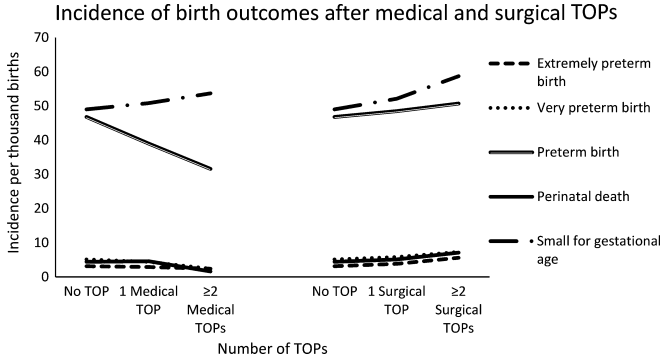

Figure 1. Risk of adverse perinatal outcomes after medical and surgical TOPs per 1000 births.

Table 2. Perinatal outcomes among women with singleton births having previous induced TOPs by the number and methods of TOPs in 1996–2013 in Finland

	One abortion versus no TOP		More than one abortions versus no TOP	
Perinatal outcomes	One medical TOP vs. no TOP OR (95% CI)	One surgical TOP vs. no TOP OR (95% CI)	More than one medical TOPs vs. no TOP OR (95% CI)	More than one surgical TOPs vs. no TOP OR (95% CI)
Extremely preterm birth				
Unadjusted model	0.93 (0.66, 1.30)	1.23 (1.02, 1.47)	0.76 (0.24, 2.35)	1.84 (1.25, 2.70)
Adjusted model[a]	0.96 (0.68, 1.35)	1.11 (0.92, 1.33)	0.82 (0.26, 2.58)	1.51 (1.03, 2.23)
Very preterm birth				
Unadjusted model	0.87 (0.66, 1.14)	1.16 (1.00, 1.34)	0.46 (0.15, 1.43)	1.45 (1.04, 2.03)
Adjusted model[a]	0.92 (0.70, 1.21)	1.01 (0.87, 1.18)	0.50 (0.16, 1.55)	1.14 (0.81, 1.59)
Preterm birth				
Unadjusted model	0.83 (0.75, 0.91)	1.04 (0.99, 1.10)	0.66 (0.48, 0.91)	1.09 (0.96, 1.25)
Adjusted model[a]	0.85 (0.77, 0.93)	0.99 (0.94, 1.05)	0.70 (0.51, 0.96)	1.00 (0.88, 1.14)
Perinatal death				
Unadjusted model	0.96 (0.74, 1.26)	0.87 (0.74, 1.02)	2.82 (0.70, 11.30)	0.63 (0.44, 0.88)
Adjusted model[a]	0.91 (0.69, 1.19)	1.02 (0.87, 1.19)	2.52 (0.63, 10.10)	0.82 (0.58, 1.16)
SGA infant				
Unadjusted model	0.96 (0.88, 1.04)	0.94 (0.89, 0.98)	0.91 (0.71, 1.16)	0.82 (0.73, 0.93)
Adjusted model[a]	1.05 (0.97, 1.15)	1.07 (1.02, 1.13)	1.05 (0.82, 1.34)	1.07 (0.95, 1.21)

Adjusted model[a] - adjusted for maternal characteristics (maternal age, marital status, maternal smoking, maternal residence of municipality and birth year of child).

consider the number of TOPs. In this present study, we determined the risks for different adverse perinatal outcomes (preterm birth, perinatal death, and small for gestational age) after the previous single or repeated medical and surgical induced TOP(s) using the large dataset with multiple categories of TOPs by their type.

In this study, we were able to adjust for the important confounders such as; maternal age, urbanity of residence, marital or cohabiting status, maternal smoking, and the year of birth of a child, the year of last TOP, and the gestational age at TOP.

Limitations of the data

Since we have no information on TOPs before 1983, some women with first-time singleton birth might be misclassified into no TOP group. However, we assume that are very few such cases and will be unlikely to affect our results. In this study, we could not adjust for some important confounders such as interpregnancy interval and socio-economic status because of incomplete information in our data and the problems to define a socio-economic status for young women, of them many are still in education or at

Table 3. Perinatal outcomes among women with first birth after their repeat medical, surgical or both induced TOPs in Finland during 1983–2013

Perinatal outcomes	More than one surgical TOPs vs. more than one medical TOPs OR (95% CI)	More than one both TOPs (medical and surgical) vs. more than one medical TOPs OR (95% CI)	More than one medical TOPs vs. one medical TOP OR (95% CI)	More than one surgical TOPs vs. one surgical TOP OR (95% CI)
Extremely preterm birth				
Unadjusted model	2.43 (0.74, 8.04)	1.96 (0.54, 7.02)	0.81 (0.25, 2.65)	1.50 (0.99, 2.27)
Adjusted model[a]	1.06 (0.25, 4.39)	0.95 (0.24, 3.74)	1.09 (0.33, 3.66)	1.35 (0.88, 2.07)
Very preterm birth				
Unadjusted model	3.15 (0.97, 10.28)	1.78 (0.49, 6.47)	0.53 (0.16, 1.69)	1.25 (0.87, 1.80)
Adjusted model[a]	1.74 (0.43, 7.02)	1.18 (0.30, 4.65)	0.60 (0.18, 1.97)	1.09 (0.76, 1.58)
Preterm birth				
Unadjusted model	1.65 (1.17, 2.32)	1.40 (0.97, 2.03)	0.80 (0.58, 1.11)	1.05 (0.91, 1.21)
Adjusted model[a]	1.21 (0.79, 1.86)	1.24 (0.84, 1.83)	0.81 (0.58, 1.12)	1.03 (0.89, 1.18)
Perinatal death				
Unadjusted model	0.22 (0.05, 0.93)	0.29 (0.06, 1.29)	2.92 (0.71, 11.98)	0.72 (0.50, 1.04)
Adjusted model[a]	0.44 (0.09, 2.22)	0.51 (0.41, 9.41)	2.72 (0.65, 11.32)	0.86 (0.59, 1.25)
SGA infant				
Unadjusted model	0.91 (0.69, 1.19)	0.29 (0.06, 1.29)	1.06 (0.82, 1.37)	1.13 (0.99, 1.29)
Adjusted model[a]	1.25 (0.87, 1.80)	0.51 (0.11, 2.42)	0.98 (0.75, 1.27)	0.98 (0.86, 1.12)

Adjusted model[a] - adjusted for maternal characteristics (maternal age, marital status, maternal smoking, maternal residence of municipality and year of birth), gestational age at TOP and year of last TOP.

home with a child(ren). Smoking has been found to be a good proxy for socio-economic status in Finland,[25] and thus we also employed it.

Interpretation

In keeping line with earlier studies,[11,19,25,26] we found the demographic characteristics of the first-time mothers who had previous induced TOP different from those first-time mothers having no history of induced TOP. As in previous studies,[5,8,9,11,27,28] during the time period where most of the induced TOPs were surgical, our study found an increased risk for extremely preterm birth among the women with at least two surgical induced TOPs compared to the women with no history of induced TOP. In contrast to some previous studies,[5,7,8,27,28] we did not find any significant increased risk for preterm birth after one surgical or medical induced TOP; however, this is similar to the finding of a previous study from Finland.[11] A Chinese study[14] classified the women according to the method and number of induced TOPs and found an increased risk for preterm births after the multiple surgical TOPs, which is similar to the findings of our study. However, the Chinese study was based on self-reported questionnaires and might have chances of under-reporting and recall biases, and it examined risk only for one single outcome, preterm birth.

Very few studies have considered the small for gestational age and perinatal deaths. We looked for the impacts of prior TOP in SGA infants and found the associated increased risk for SGA after one surgical induced TOP. Conversely, some previous studies could not find any significant association between SGA and previously induced TOPs.[5,19] The biological mechanisms that might be responsible for the increased risk of SGA after the previous surgical termination of pregnancy are the cervical insufficiency from dilatation and curettage, post-abortion complications such as uterine adhesions and infection. However, the biological plausibility is unclear and this might be a chance finding.

Compared to the women with no history of TOP, our results of reduced risk of preterm birth among women who had undergone a previous medical TOP (s) are in line with a previous Chinese study.[29] It could be explained by the fact that women who had undergone TOPs will be more likely to be fertile yielding the better outcomes among those women having had medical TOPs when compared to those without any history of TOPs. In addition, medical TOPs cause less trauma to the cervix than the surgical ones.[7,12,30]

In line with our previous (unpublished) study and an earlier Finnish study,[11] this study found no significant association between perinatal deaths and previous induced TOP(s).

In keeping line with the earlier Chinese study,[14] we found significantly higher risk for preterm birth when comparing the women having had at least two surgical TOPs with those having had at least two medical TOPs; however, the significance was disappeared in our study when adjusted for confounders. As in the Chinese study, we found an increased risk for the very preterm birth but the risk was not significant. A Danish study using the registered data reported no increased risk of preterm births after the medical TOP compared to the surgical one.[16] However, the Danish study did not differentiate between single or repeated induced TOPs and the results might be weakened by the self-reported exposures on previous induced TOPs.

Many studies have proved the increased risk of preterm birth with the additional number of prior induced TOPs,[5–11] but none of these studies differentiated the number of induced TOPs by the method of TOP. We did the subgroup analysis comparing the women with one medical TOP to repeat medical TOPs and women with one surgical TOP to repeat surgical TOPs after adjusting for important confounders; however, our findings did not suggest associated significant risk in any adverse perinatal outcomes.

Conclusions

Adverse perinatal outcomes in the first-born child of a woman are associated with repeat surgical induced TOPs. The information on the risk of preterm birth and SGA after repeat surgical TOPs will be of high importance for health professionals while counselling women after first TOP. Sexual health education should include the consequences of repeat induced TOPs and promotion of using contraceptives immediately after first TOP.

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PUBLICATION 3

The duration of gestation at previous termination of pregnancy and its impacts on subsequent birth- a nationwide registry-based study.

Situ KC, Mika Gissler, Reija Klemetti

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The duration of gestation at previous induced abortion and its impacts on subsequent births: A nationwide registry-based study

Situ KC[1] | **Mika Gissler**[2,3] | **Reija Klemetti**[4]

[1]Faculty of Social Sciences, University of Tampere, Tampere, Finland

[2]Department of Information Services, Finnish Institute for Health and Welfare, Helsinki, Finland

[3]Department of Neurobiology, Care Sciences and Society, Division of Family Medicine, Karolinska Institute, Stockholm, Sweden

[4]Department of Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland

Correspondence
Situ KC, Faculty of Social Sciences, Health Sciences, University of Tampere, Tampere 33014, Finland.
Email: situ.kc@tuni.fi; situkc11@gmail.com

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Abstract

Introduction: Previous induced abortions have been associated with adverse birth outcomes. However, only a few studies have considered the possible influence of gestational age at induced abortion. Therefore, this study aimed to identify the impacts of gestational age during prior induced abortion(s) on subsequent births among first-time mothers in Finland.

Material and methods: First-time mothers (n = 418 690) with singleton births between 1996 and 2013 were identified from the Finnish Medical Birth Register and linked to the Abortion Register. Logistic regression analysis was used to estimate the risk (odds ratio [OR] and 95% confidence interval [CI]) of birth outcomes such as prematurity, low birthweight, perinatal death and small for gestational age (SGA).

Results: Higher risk was determined for extremely preterm birth (OR 2.28; 95% CI 1.53-3.39) and very low birthweight (OR 1.62; 95% CI 1.22-2.16) in women having had late-induced abortion(s) (≥12 gestational weeks) compared with women having had early-induced abortion(s) (<12 gestational weeks); after adjusting for women's background characteristics, abortion method and interval between the pregnancies. When the analysis was limited to a single abortion, an increased risk was found for extremely preterm birth (OR 1.71; 95% CI 1.02-2.81). Higher risks were found for extremely preterm (OR 4.09; 95% CI 2.05-8.18) and very low birthweight (OR 2.65; 95% CI 1.61-4.35) among women with two or more late-induced abortions compared with those with two or more early-induced abortions. Worse outcomes were seen after a late-induced abortion compared to an early-induced abortion for both medically and surgically induced abortion.

Conclusions: The risk of subsequent adverse birth outcomes is very small if any, but the risk is higher with increasing gestational age at the time of induced abortion. Our study supports reduction of unintended pregnancy and offering abortion services without delay and as early in gestation as possible.

KEYWORDS
gestational age, induced abortion, perinatal outcomes, register-based study, termination of pregnancy

Abbreviations: AR, abortion register; CI, confidence interval; MBR, medical birth register; OR, odds ratio; SGA, small for gestational age; THL, National Institute for Health and Welfare; TOP, termination of pregnancy.

1 | INTRODUCTION

Induced abortion (hereafter abortion) is one of the most common gynecologic procedures performed in women of reproductive age.[1] The estimated rate of abortion in developed countries is 27 per 1000 women belonging to the reproductive age group. Even in countries with high-quality and reliable health services, abortion may lead to adverse birth outcomes, which could have significant public health implications.[2-5]

In Finland, almost 92% of induced abortions were carried out in the first trimester of gestation, and 96% were performed on social grounds in 2015.[6] According to Finnish abortion legislation, an abortion can be performed up to 20 weeks of gestation for social, medical and ethical reasons (such as rape or incest), and up to 24 weeks of gestation in cases of confirmed adverse medical condition of the fetus. Approval from one or two physicians is required up to 12 weeks; an approval from a national authority is required in cases of fetal abnormality and after 12 weeks of gestation.[7]

It has been suggested that advanced gestational age at abortion is linked to increased complications.[8,9] In the USA, the risk of abortion-related death increased by 38% for each additional week of gestation between 1988 and 1997.[8] However, the study was based on surgical abortions.[8] Second-trimester medical termination was associated with immediate complications, which did not increase with advancing gestational age.[9] The grounds for delayed abortion varied, including considerable strain caused by living or other conditions, young age, fetal indications and maternal health indications.[10,11]

There is evidence that a higher number of previous abortions is associated with an increased risk of adverse perinatal outcomes in a subsequent pregnancy.[2-5,12-14] The increased risk has been associated with prior surgical abortions but not with the medical ones.[5,15,16] However, very few studies have explored the long-term consequences of gestational weeks at previous abortion in subsequent birth.[17,18]

Some previous studies suggested that abortions in the second trimester were not associated with increased risk of preterm birth in the subsequent birth. Most of these studies were based on surgical abortions.[15,18-21] A Finnish study assessing short-term complications reported a higher risk of surgical evacuation and infection after second-trimester than after first-trimester medical abortion.[9] A recent large-scale study found no increased risk of adverse outcomes in subsequent deliveries when comparing second-trimester abortion to first-trimester abortion.[19,20]

Hence, previous studies are limited and there is a need to explore whether the perinatal risk is associated with previous abortions by their gestational age at the time of the procedure. The present study, therefore, aims to investigate the impact of the duration of gestation at previous induced abortions on subsequent birth outcomes among Finnish first-time mothers with a singleton birth.

Key message

The risk of adverse birth outcomes was higher with increasing gestational age at induced abortion. Poorer birth outcomes were found among women with late-induced abortion compared with those with early-induced abortion, and an increased risk after late-induced abortion was also found when analyzed by the method of abortion.

2 | MATERIAL AND METHODS

The Finnish Medical Birth Register (MBR) and the Abortion Register (AR), maintained by the National Institute for Health and Welfare, were used in this study. Since 1987, the Finnish MBR has kept records of all information of newborns and mothers, including the mother's background characteristics, care during pregnancy and delivery, and newborn postnatal care up to 1 week. The AR was started in 1950 but computerized data on all abortions is only available from 1983. The physicians performing the abortion procedure are obliged to report the case to the AR using a specific form. The AR contains information on the woman's background, gestational age, indications for abortions, dates, procedures and complications occurring during the procedure. The information contained in both registries is complete and highly reliable.[22]

First-time mothers with singleton births from 1996 to 2013 were identified from the MBR and were linked to the AR (1983-2013) to obtain information regarding previous abortions. The study population was divided into three groups: no prior induced abortion, early-induced abortion (<12 weeks) and late-induced abortion (≥12 weeks), according to the gestational age during the prior induced abortion. In cases where the woman had gone through several abortions, the classification was based on the most recent abortion. Since most of the induced abortions were reported in women with less than 12 weeks of gestation, the study population was further categorized into four groups for additional analysis: no induced abortion, induced abortion before 8 weeks, induced abortion between 8 and 12 weeks, and induced abortion after 12 weeks.

The outcome measures were retrieved from the MBR. The gestational age at birth was determined by the date of the last menstruation, confirmed using ultrasonography in early pregnancy. Preterm birth was defined as birth before 37 completed weeks of gestation, very preterm birth as birth before 32 weeks of gestation, and extremely preterm birth as birth before 28 weeks of gestation. Low birthweight was defined as birthweight of less than 2500 g, and very low birthweight as birthweight of less than 1500 g. SGA was defined as the birthweight and/or more than two standard deviations (SD) below the sex- and gestational age-specific reference mean.[23] Perinatal death was defined as death occurring from 22 weeks of gestation to 1 week postnatally.

Cases where gestational age at birth (n = 1004, .2%), birthweight (n = 105, .03%) and gestational age at abortion (n = 5, .0%)

were missing, and where there were illogical values for interval between pregnancies (n = 60, .0%), were excluded from the study. In some cases, dates of induced abortions were either incomplete or missing in the dataset (n = 3964, 7.3%), and they were also excluded from the regression analysis. As late abortions were performed mostly for medical reasons, we excluded those abortions that were performed due to medical reasons (n = 1441, 2.65%) when comparing birth outcomes after late and early abortion. These medical reasons include cases where pregnancy is a risk to the woman's life or health, and suspected or confirmed anomaly or illness of the fetus.

2.1 | Statistical analyses

All the data was analyzed using STATA version 14 (StataCorp). Cross-tabulations were performed for the descriptive analysis and chi-square tests were used to determine differences between the study groups. Differences between the early and the late abortion group were tested using relative tests for proportion. The level of statistical significance was set at $P < .05$. Logistic regression analysis (odds ratio [OR] and 95% confidence interval [CI]) was performed, with adjustment for confounders. The known risk factors and statistically significant variables were added as confounders in multivariable analysis.

Several comparisons were made between the study groups. First, the birth outcomes among women with previous early and late abortion were compared with those in women without prior abortion and then with each other, adjusting for potential confounders. The confounders, such as maternal age, municipality of residence and smoking status were adjusted for when comparing early and late abortion with no abortion. Additional adjustments were made for the method of abortion, number of abortions and interval between pregnancies when comparing late abortion with early abortion.

Next, the risk of duration of gestation at previous abortion in subsequent birth was assessed in women having had one prior abortion and those having had two or more (≥2) prior abortions. The risk of adverse birth outcomes was compared between those women having had one late abortion with those having had one early abortion, adjusting for the confounders. Likewise, the risk of birth outcomes among women having had two or more (≥2) late abortions was compared with those having had two or more (≥2) early abortions. A sub-analysis was also performed separately among women having had one medical and one surgical abortion to determine the difference in adverse birth outcomes between early and late abortion.

2.2 | Ethical approval

Approval for the study was obtained from the ethical committee of National Institute for Health and Welfare (THL) (date: 22 October 2009), and permission was granted by THL to use the register data for this study (date: 22 October 2014).

3 | RESULTS

The present study included 418 690 first-time mothers with a singleton birth between 1996 and 2013. Of them, 364 392 (87.0%) women had no history of prior induced abortion, 46 589 (11.1%) had early-induced abortion and 7709 (1.8%) had late-induced abortion. Women having had early abortions were younger and less often smokers than those women who had late abortions (Table 1). The abortions performed in early gestation were based more on social indications and performed using surgical procedures (Table 1). An increased incidence of adverse birth outcomes was seen more often among women with late abortions than among women with no abortion or early abortion (Table 2).

When compared with women having had no abortion, those having had an early abortion had a slight but significantly increased risk of having a small for gestational age birth, after adjusting for potential confounders (Table 3). In the adjusted regression analysis, women having had a late abortion showed a significantly increased risk of extremely preterm birth, very preterm birth, very low birthweight and small for gestational age birth, and a significantly decreased risk of perinatal death, as compared with those having had no abortion (Table 3).

When excluding termination of pregnancy (TOP) performed for medical reasons, women having had a late abortion had a 2.3-fold and 1.6-fold significantly increased risk of extremely preterm birth and very low birthweight compared with women having had an early abortion, after adjusting for confounders (Table 3). When the analysis was performed among women who had had only one abortion, significantly increased risk was only found for extremely preterm birth, adjusted for confounders (Table 3). When compared with women with ≥2 early abortions, those with ≥2 late abortions had a 4.1-fold and 2.6-fold significantly increased risk of extremely preterm birth and very low birthweight (Table 3). A significant reduction in the risk of perinatal death was found among women with late abortion(s) and ≥2 late TOPs when compared with those with early abortion(s) and ≥2 early abortions.

When the analysis was performed separately for those abortions that were performed medically and surgically, a 1.4-fold significantly increased risk was found for both preterm birth and low birthweight among women having had a late medical abortion compared with women who had early medical abortion, after adjusting for confounders. When compared to women with an early surgical abortion, women who had had a late surgical abortion had a 2.6-fold and 1.5-fold significantly increased risk of extremely preterm birth and very low birthweight (Table 4). A significantly increased risk of extremely preterm birth and very low birthweight was found among women having had an abortion at ≥13 weeks of gestation compared with women having had an abortion before 8 weeks of gestation, after adjusting for confounders (Table 4).

TABLE 1 Background characteristics of first-time Finnish mothers by gestational weeks at previous induced abortion between 1996 and 2013, n (%)

Background variables	No previous induced abortion 364 392 (87.0)	Early-induced abortion (<12 weeks) 46 589 (11.1)	Late-induced abortion (≥12 weeks) 7709 (1.8)	Total 418 690
Age, years				
<20	21 094 (5.8)	2460 (5.3)	506 (6.6) *	24 060 (5.8)
20-24	89 270 (24.5)	12 078 (25.9)	2073 (27.0)*	103 421 (24.7)
25-29	134 430 (36.9)	15 251 (32.7)	2327 (30.1)*	152 008 (36.3)
30-34	86 232 (23.6)	11 239 (24.1)	1772 (22.9)*	99 243 (23.7)
35-39	27 948 (7.7)	4543 (9.8)	789 (10.2)	33 280 (7.9)
≥40	5418 (1.5)	1018 (2.2)	242 (3.1)*	6678 (1.6)
Residence				
Urban	259 140 (71.1)	34 275 (73.6)	5585 (72.4)*	299 000 (71.4)
Semi-urban	51 876 (14.2)	6212 (13.3)	1098 (14.3)*	59 186 (14.1)
Rural	51 156 (14.1)	5896 (12.7)	993 (12.9)	58 045 (13.9)
Abroad	2220 (.6)	206 (.4)	33 (.4)	2459 (.6)
Marital status				
Married/cohabiting	313 584 (86.0)	36 228 (77.8)	5964 (77.4)	355 776 (85.0)
Unmarried/single	45 859 (12.6)	9548 (20.5)	1606 (20.8)	57 013 (13.6)
Others	4949 (1.4)	813 (1.7)	139 (1.8)	5901 (1.4)
Smoking status during pregnancy				
Did not smoke	301 450 (82.7)	31 050 (66.6)	4840 (62.8)*	337 340 (80.6)
Quitted smoking during first trimester	17 617 (4.8)	3745 (8.1)	578 (7.5)	21 940 (5.2)
Smoked after first trimester	38 289 (10.5)	10 806 (23.2)	2122 (27.5)*	51 217 (12.2)
Unknown	7036 (2.0)	988 (2.1)	169 (2.2)	8193 (2.0)
Indication for induced abortion				
Social		46 589 (99.7)	6350 (82.4)*	52 817 (97.3)
Medical (women)		65 (.1)	35 (.5)*	100 (.2)
Medical (foetus)		20 (.1)	1321 (17.1)*	1341 (2.5)
Ethical		37 (.1)	3 (.0)*	40 (.0)
Method of induced abortion				
Medical		10 302 (22.1)	3080 (39.9)*	13 382 (24.7)
Surgical		34 812 (74.7)	3703 (48.1)*	38 515 (70.9)
Both		1475 (3.2)	926 (12.0)*	2401 (4.4)

*P value <.05 for tests for relative proportion, late-induced abortion group is compared with early-induced abortion group.

4 | DISCUSSION

We found a higher risk of adverse birth outcomes after induced abortion at a later gestational age than induced abortion at an early gestational age. An increased risk of extremely preterm birth and very low birthweight was found among women with late abortion(s) when compared with those with early abortion(s). When the analysis was restricted to only one abortion, women who had had a late abortion showed a higher risk of only extremely preterm birth compared to women who had experienced an early abortion. An increased risk was found for extremely preterm birth and very low birthweight among the women with ≥2 late abortions when compared with those with ≥2 early abortions. An increased risk of adverse birth outcomes was found after one late abortion compared with one early abortion in both medical and surgical abortions.

This is a large study including all Finnish first-time mothers from 1996 to 2013, which explored adverse birth outcomes after previous abortion by gestational weeks during the abortion. This study was based on national registers, the Medical Birth Register and the Abortion Register with confirmed high quality.[22] All births since 1996 were selected in order to include information on previous induced abortions of as many women as possible. However, no information was available on the women who had abortions before 1983 or who had terminations performed in other countries. Since the information on abortions was from a long time period there were abortions with missing dates. Therefore, it is difficult to identify the

TABLE 2 Risk of adverse birth outcomes according to gestational age at induced abortion among first-time Finnish mothers between 1996 and 2013

Birth outcomes	No previous induced abortion (n = 364 392)	Early-induced abortion (<12 weeks) (n = 46 589)	Late-induced abortion (≥12 weeks) (n = 7709)	*P* value	Total (n = 418 690)
Extremely preterm birth	1120 (3)	149 (3)	54 (7)*	<.05	1323 (3)
Very preterm birth	1843 (5)	236 (5)	63 (8)*	<.05	2142 (5)
Preterm birth	17 033 (47)	2122 (46)	371 (48)	.43	19 526 (47)
Very low birthweight	2795 (8)	350 (8)	100 (13)*	<.05	3245 (8)
Low birthweight	12 396 (34)	1656 (36)*	288 (38)*	.38	14 340 (34)
Perinatal death	1600 (4)	215 (5)*	60 (8)*	<.05	1875 (5)
Small for gestational age	16 934 (46)	2327 (49)*	379 (49)	1.00	19 640 (47)

Note: Data presented as n (per thousand births).

P value <.05 from tests for relative proportion in comparing late-induced abortion with early-induced abortion group.

**P* value <.05 from tests for relative proportion in comparing early- and late-induced abortions with no abortion group.

exact timing of abortion in cases of repeat abortion, and those abortions were excluded from the study. In our study, we have classified study groups as women undergoing medical abortion only, surgical abortion only and both (medical and surgical) abortion. In the last category (both), we could not identify abortions performed by medical methods followed by surgical methods because the AR only includes information on successful abortions. We were not able to use the Hospital Discharge Register, since medical abortions are not registered. The Primary Health Care Register could have been used, but we were not able to use it as a data source, as it was established in 2011 and the register was not complete before 2013.

The demographic profiles of women having had previous abortions differed from those who did not have any history of abortion, and this was consistent with the previously published literature.[4,5,24,25] In the present study, smoking was found to be more common among women with late abortion(s) when compared with those with early abortion(s). Based on the previous literature available and the quality in healthcare registers, the potential confounders were listed as maternal age, marital status, smoking status, number of previous abortions, the method of previous abortion and the interval between pregnancies. These confounders were adjusted in the logistic regression. However, the socioeconomic status of women could not be adjusted for, because of the incomplete data available in the registers. It is difficult to define the socioeconomic status of a young woman, such as that of a housewife or a student. Hence, smoking status was used as a proxy for socioeconomic status.[26] Also, we could not consider the pre-existing health conditions of the women because the dataset we used (extracted from Finnish registers) did not include that information.

Many previous studies revealed that abortions have been associated with perinatal risk.[3-5,13] However, very few studies explored the risk of second-trimester abortion on subsequent birth.[17-21,27] Of the few studies available, some were based on surgical abortion,[17,18,21] and very few were based on medical abortion.[20,27] Most of them were limited by small sample size or lack of a comparison group, and others lack the adjustments for potential confounders such as smoking, interval between pregnancies and methods of abortion.[17-19,21] This study is the largest of its kind that could partly control for the potential confounders with more birth outcomes. It is likely that medical indications for late abortion(s) might affect subsequent birth outcomes. Therefore, in this study, we excluded women whose abortions were performed for medical reasons in regression analysis when making comparisons between early and late abortion(s). However, this may also introduce bias, as only women requesting late abortion on social and ethical grounds are left. These women may differ from those seeking early abortions and have other risk factors for adverse birth outcomes that cannot be controlled for.

In line with a previous study from Scotland,[19] we found insignificant risks for preterm birth and low birthweight among women who had experienced early abortion compared with those who had had no abortion. A significantly increased risk of extremely preterm birth, very preterm birth and very low birthweight was identified among those women who had had late abortions when compared with those who had had no prior abortion, in contrast to the results of previous studies.[17-21] However, most of the previous studies were based on surgical abortion; there were no control groups in a few previous studies,[17,21] and adjustments were not made for all potential confounders in these studies.

In our study, a higher risk of extremely preterm birth and very low birthweight was observed after previous late abortions compared with early abortions, and also for women with ≥2 previous abortions. When analysis was performed separately among women having had medical and surgical abortions, an increased risk of preterm birth and low birthweight was found after a late abortion compared with an early abortion. Very few prior studies compared the risk for women with previous early and late abortion,[18,19] and none distinguished between single and multiple abortions. Those earlier studies found no difference in the risk of adverse birth outcomes among women who had had early and late abortions,[18,19] which contrasts with the results of the present study. The higher risk of cervical incompetence among women undergoing several abortions at later gestation might explain the increased risk of adverse outcomes.[28] However, in our study we

TABLE 3 Risks of adverse birth outcomes by gestational weeks at previous induced abortion among first-time Finnish mothers between 1996 and 2013

	Early-induced abortion vs no abortion		Late-induced abortion vs no abortion		Late vs early-induced abortion[d]		One late-induced abortion vs one early induced abortion[d]		≥2 late-induced abortions vs ≥2 early-induced abortions[d]	
	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[b]	Crude	Adjusted[c]	Crude	Adjusted[c]
Birth outcomes	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Extremely preterm birth	1.04 (.87-1.23)	.97 (.82-1.16)	2.29 (1.75-3.02)	2.06 (1.56-2.73)	1.88 (1.30-2.73)	2.28 (1.53-3.39)	1.41 (.86-2.32)	1.71 (1.02-2.81)	2.93 (1.53-5.60)	4.09 (2.05-8.18)
Very preterm birth	1.00 (.87-1.14)	.91 (.79-1.05)	1.63 (1.27-2.09)	1.46 (1.13-1.88)	1.33 (.93-1.88)	1.37(.95-1.99)	1.27 (.83-1.95)	1.27 (.81-1.99)	1.40 (0.73-2.67)	1.69 (0.86-3.33)
Preterm birth	.97 (.93-1.02)	.95 (.90-.99)	1.04 (.93-1.15)	1.00 (.90-1.11)	1.04 (.91-1.18)	1.05(.91-1.20)	1.04 (.89-1.22)	1.05 (.90-1.24)	1.02 (0.79-1.30)	1.02 (0.79-1.32)
Very low birthweight	.98 (.87-1.09)	.89 (.79-1.00)	1.71 (1.39-2.09)	1.50 (1.22-1.84)	1.49 (1.13-1.96)	1.62 (1.22-2.16)	1.21 (.85-1.73)	1.28 (.89-1.86)	2.05 (1.28-3.29)	2.65 (1.61-4.35)
Low birthweight	1.04 (.99-1.10)	.94 (.90-1.00)	1.11 (.98-1.24)	.97 (.86-1.09)	1.07 (.93-1.24)	1.07 (.92-1.24)	1.07(.90-1.28)	1.10 (.92-1.31)	1.03 (0.79-1.36)	0.99 (0.75-1.32)
Perinatal death	.95 (.82-1.09)	1.05 (.91-1.21)	.56 (.43-.74)	.64 (.49-.84)	.60 (.43-.83)	.55 (.39-.78)	.73(.48-1.12)	.74 (.48-1.16)	0.40 (0.22-0.72)	0.30 (0.16-0.56)
Small for gestational age	.93 (.89-.97)	1.06 (1.01-1.11)	.94 (.85-1.05)	1.13 (1.02-1.25)	.96 (.85-1.08)	1.03 (.90-1.17)	1.05 (.90-1.23)	1.10 (.94-1.29)	0.85 (0.68-1.06)	0.88 (0.71-1.11)

Note: Missing cases for interval between pregnancies (n = 3964 [7.3%]) were excluded from the analysis.

[a]Adjusted for maternal age, maternal residence, marital status and maternal smoking status.

[b]Adjusted for maternal age, residence, maternal smoking status, method of induced abortion, number of induced abortion and interval between pregnancies.

[c]Adjusted for maternal age, residence, maternal smoking status, method and interval between the pregnancies.

[d]Analysis was performed excluding those women whose induced abortion was performed for medical indications.

TABLE 4 Risk for adverse birth outcomes by gestational age and method among the first-time Finnish mothers between 1996 and 2013

	Early- and late-induced abortion by the method[a]				Induced abortion at different gestational age vs <8 weeks of gestation[c]			
	Late vs early medical induced abortion		Late vs early surgical induced abortion		8-12 weeks vs <8 weeks of gestation		≥13 weeks vs <8 weeks of gestation	
Birth outcomes	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	Crude OR (95% CI)	Adjusted[d] OR (95% CI)	Crude OR (95% CI)	Adjusted[d] OR (95% CI)
Extremely preterm birth	1.76 (.75-4.14)	1.62 (.64-4.12)	2.15 (1.38-3.34)	2.61 (1.67-4.09)	1.56 (1.02-2.40)	1.28 (.79-2.06)	2.35 (1.27-4.36)	2.83 (1.44-5.55)
Very preterm birth	1.55 (.76-3.15)	1.58 (.77-3.24)	1.31 (.84-2.04)	1.26 (.79-2.01)	1.25 (.89-1.73)	1.05 (.73-1.50)	1.26 (.71-2.23)	1.36 (.75-2.46)
Preterm birth	1.49 (1.19-1.88)	1.43 (1.13-1.81)	.89 (.74-1.06)	.88 (.73-1.06)	1.07 (.97-1.20)	.97 (.86-1.09)	1.11 (.92-1.35)	1.11 (.91-1.36)
Very low birthweight	1.82 (1.06-3.12)	1.73 (.99-3.01)	1.42 (1.00-2.02)	1.51 (1.05-2.16)	1.26 (.96-1.64)	1.04 (.77-1.39)	1.67 (1.09-2.56)	1.79 (1.14-2.81)
Low birthweight	1.45 (1.13-1.87)	1.43 (1.11-1.85)	.89 (.73-1.10)	.88 (.71-1.08)	1.09 (.97-1.23)	1.01 (.88-1.15)	1.06 (.85-1.32)	1.05 (.83-1.32)
Perinatal death	.49 (.27-.92)	.51 (.27-.98)	.61 (.40-.93)	.57 (.37-.88)	.96 (.70-1.32)	1.13 (.79-1.61)	.63 (.38-1.05)	.62 (.36-1.06)
Small for gestational age	1.02 (.81-1.27)	1.12 (.89-1.41)	1.03 (.87-1.22)	1.07 (.90-1.28)	.95 (.86-1.05)	.99 (.89-1.11)	.92 (.76-1.10)	1.03 (.85-1.24)

Note: Missing cases for interval between the pregnancies (n = 3964 (7.3%)) were excluded during the analysis.

Analysis was performed excluding those women whose induced abortion was performed on medical indications.

Missing cases for interpregnancy interval (n = 3964 (7.3%)) were excluded during the analysis.

[a]Analysis performed among the women having had only one induced abortion.

[b]Adjusted for maternal age, maternal residence, maternal smoking and interpregnancy interval.

[c]Analysis performed among the women having had induced abortion at different gestational age, where gestational week <8 weeks was treated as a reference for each studied group.

[d]Adjusted for maternal age, residence, smoking, number of induced abortion, method of induced abortion and interval between the pregnancies.

could not distinguish between women with medical abortion only, medical abortion with surgical intervention or surgical abortion only. It is likely that these methods carry different risks of subsequent cervical incompetence.

A reduced risk was seen for perinatal death when comparing late abortion vs no prior abortion, late abortion vs early abortion and at least two late abortions vs at least two early abortions. A German study reported no significantly increased risks of perinatal death after a previous abortion, which is consistent with the findings of the present study.[29] However, the sample size of that study was small, previous abortions may have been underreported, and the study did not control for pregnancy intervals. Moreover, perinatal death is a rare outcome and is less studied in terms of previous abortions. Therefore, an even larger dataset would be required to confirm the findings of the present study.

The present study found no association between SGA and early or late abortion, although there was an increased risk of SGA after early and late abortion than no abortion. An earlier Italian study[30] found conflicting results, with no increased risk of SGA after abortion.[30] That study had several limitations, such as no consideration for the methods of abortion, no differentiation between legal and illegal abortions, and possible selection bias in the control group.[30] However, the biological plausibility for the association between SGA and previous abortion is still unclear.

5 | CONCLUSION

The risk of subsequent adverse birth outcomes after early-induced abortion is very small, if any, but the risk is higher with increasing gestational age at the time of induced abortion. An increased risk of subsequent adverse birth outcomes was also found after late-induced abortion compared with after early-induced abortion irrespective of abortion method. Our study suggests preventing unintended pregnancies by offering more effective contraceptive services and abortion services without delay so that women can terminate their pregnancy as early as possible if required.

CONFLICT OF INTEREST

None.

ORCID

Situ KC https://orcid.org/0000-0002-1026-4494

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Factors influencing the risk of repeat termination of pregnancy: A register-based study in Finland

Situ KC, Mika Gissler, Anna Heino, Reija Klemetti

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Factors influencing the risk of repeat termination of pregnancy: A register-based study in Finland

Situ KC [a,*], Mika Gissler [b,c], Anna Heino [b], Reija Klemetti [d]

[a] Faculty of Social Sciences, Tampere University, FI-33014 Tampere, Finland
[b] Department of Knowledge Brokers, National Institute for Health and Welfare, FI-00271 Helsinki, Finland
[c] Department of Molecular Medicine and Surgery, Karolinska Institute, Sweden and Region Stockholm, Academic Primary Health Care Centre, S-14183 Stockholm, Sweden
[d] Department of Public Welfare, National Institute for Health and Welfare, FI-00271 Helsinki, Finland

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ABSTRACT

Objective: This study aimed to assess how factors such as sociodemographic characteristics, termination of pregnancy (TOP) related factors and contraception affect the risk of repeat TOP.
Materials and method: This is a nationwide register-based study of 193,741 women who had TOP(s) during 1987–2015, using the Finnish Register of Induced Abortions. The risk of various factors, such as age, marital status, residence, parity, TOP related factors and contraception, was assessed separately for each repeat TOP. Cox proportional hazard model was used to estimate risk of different factors for repeat TOPs.
Results: 21% of the women having TOP had repeat TOPs during the years 1987–2015. Among women with repeat TOPs, more than 70% had one repeat TOP and the rest had two or more. Older, married and rural or semi-urban women had reduced risk of repeat TOPs. Adjusted risk for one repeat TOP was higher among parous women (HR 1.67, 95% CI 1.61–1.72). No significant risk for repeat TOP was observed by method in sub-analysis for the recent period after 2006. Women using less reliable (HR 1.14, 95% CI 1.06–1.23) and unreliable (HR 1.33, 95% CI 1.23–1.43) contraception had increased risk of repeat TOP than women using reliable contraception.
Conclusion: Older age, being married, residing in rural or semi-urban areas and using reliable contraception were found to be protective factors for repeat TOPs whereas, parous women had higher risk for repeat TOPs. Proper counselling regarding contraception and use of reliable contraception immediately after TOP should be encouraged.

Introduction

Termination of pregnancy (hereafter TOP) is a common procedure performed among women, that might have significant consequences for sexual and reproductive health. Earlier literature has documented that, despite minimal consequences, TOP has been linked to long-term effects, specifically preterm birth and low birth weight in subsequent births [1,2,3]. The risk of adverse birth outcomes increased with the additional number of TOPs [1,3,4]. Increased knowledge of risk factors associated with repeat TOPs is important to prevent unintended pregnancy and thus the repeat TOPs, which ultimately helps ensure the health and well-being of women. However, studies exploring the factors associated with repeat TOPs have been poorly understood and limited.

Around 73 million TOPs were performed globally each year in 2015–2019, 61% of them for unintended pregnancies [5]. The number of TOPs has remained stable or decreased over recent years in many European countries, including Finland [5,6]. Among women having had TOP, the proportion of repeat TOPs is high but varies by country. For example, repeat TOPs account for 50% of women having TOP in the United States, 43% in England and Wales, 46% in Sweden and 37% in Norway [7–10]. In Finland, 37% of women who had TOP in 2021 had gone at least one previous TOP [6], whereas, it was 26% in 1987 (unpublished data). According to the Finnish legislation dates from 1970 and 1985, a pregnancy can be terminated for social, medical or ethical grounds up to 20 weeks of gestation and up to 24 weeks, in cases of confirmed fetal anomalies [11]. Approval from one or two physician is required to terminate a pregnancy till 12th gestational week however, after 12 weeks, approval from national authority is required [11].

* Corresponding author at: Faculty of Social Sciences, Health Sciences, FI – 33014 Tampere University, Finland.
E-mail addresses: situ.kc@tuni.fi, situkc11@gmail.com (S. KC).

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Evidence from countries with high quality health services (e.g. Western Europe, USA, Canada and New Zealand) demonstrates the link between various factors and repeat TOP. Several cross-sectional studies [9,12–15] showed that repeat TOPs are associated with age, higher parity and the use of contraception, in line with the results of different prospective and register-based studies [16–20]. Other factors, such as smoking, alcohol and substance abuse, conflict with a partner and social deprivation, have also been associated with repeat TOPs [12–14,16]. Most of the existing studies are small-scale and cross-sectional, and large studies are limited. Although many studies have explored the risk of repeat TOP by sociodemographic factors [9,13,19], most have not considered the time interval between TOPs [19,20].

Using the large nationwide database, therefore, this study attempts to provide insights into how different factors such as sociodemographic factors, parity, TOP related factors and the use of contraception affect the risk of repeat TOP.

Materials and method

This is a nationwide register-based study among Finnish women who had at least one TOP during the period 1987–2015. Women having had TOP were identified from the Finnish Register of Induced Abortions, maintained by Finnish Institute of Health and Welfare (THL). The physicians who perform TOPs are obliged to report each case to the register using a specific form. The register was started in 1950, and computerized data on all TOPs are available from 1983. The register contains information on the woman's background, gestational age at TOP, indications for the TOP, dates, procedures and complications arising during the procedure. The information contained in the register is complete and highly reliable [20].

All the TOPs over the period 1987–2015 (n = 368,981) were identified from the Finnish Register of Induced Abortions. The cases with missing or incomplete personal identification code (n = 6304, 1.7%), the TOPs missing an exact date of procedure (n = 65,739, 17.8%), and those with erroneous history of procedure (n = 40,637, 13.4%) were removed from the dataset. Those cases lacking an exact procedure date were mainly during the earlier years of TOP register. Similarly, the TOPs with fetal indication (n = 6779, 1.8%) were also removed from the dataset, as these were likely to be different from TOPs with other indications (see Fig. 1).

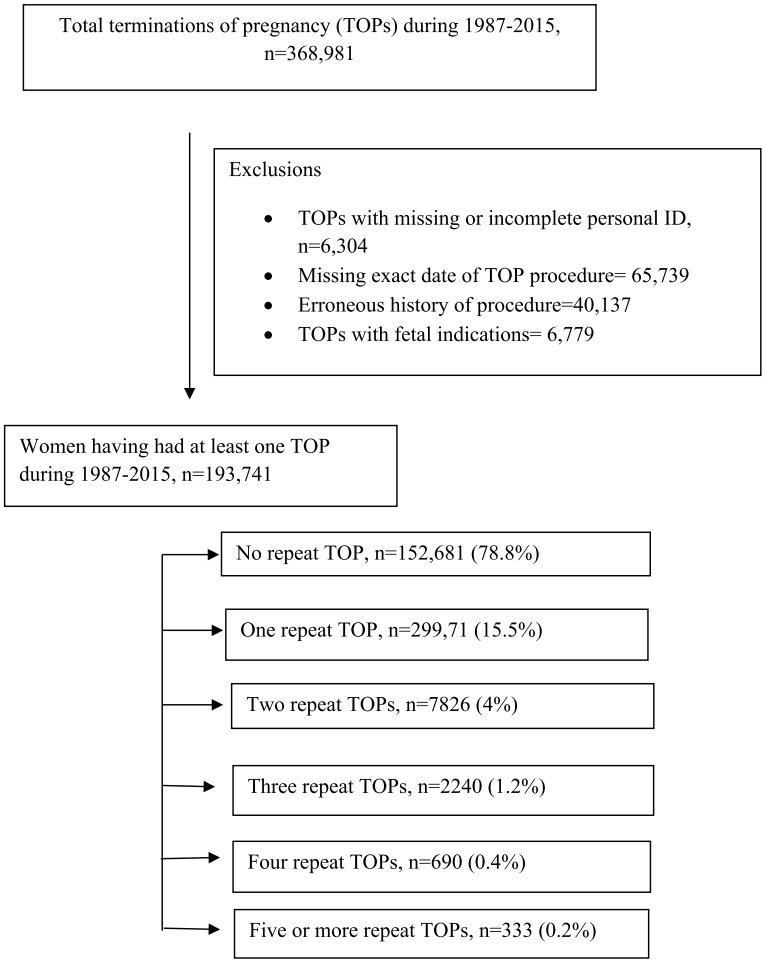

Fig. 1. A flow diagram detailing the study groups among women having had termination of pregnancy (TOP) in Finland between 1987 and 2015.

In this study, women having had at least one TOP (n = 193,741) were identified as the study cohort. Those women who had repeat TOPs were identified using the personal identification number from the Register. The women who had had the TOPs since 1987 were followed up to the end of 2015 to identify subsequent TOPs. For the sub-analysis, the most recent time-period 2006–2015 was selected based on the distribution of repeat TOPs to see how currently the different factors influence the risk of repeat TOPs.

The primary outcome for this study was the repeat TOP. Women with a history of TOP were classified according to number of TOPs as: no repeat TOP (one TOP, n = 152,681, 78.8%); one repeat TOPs (two TOPs, n = 29,971, 15.5%); two repeat TOPs (three TOPs, n = 7826, 4%); three repeat TOPs (four TOPs, n = 2240, 1.2%); four repeat TOPs (five TOPs, n = 690, 0.4%); and five or more repeat TOPs (six or more TOPs, n = 333, 0.2%). No repeat TOP was used as a comparison group.

The predictor variables were also identified using the Register of Induced Abortions. The background variables considered were the women's age, marital status and residence of municipality, parity, and TOP related characteristics, including gestational age at the TOP, grounds for the TOP, the method used, and the prior use of contraception. The urbanity of residence of municipality was classified as rural, semi-urban, urban and abroad, following Statistics Finland. Methods of contraception used before the TOP, which indicates the use at the time of conception were classified into three categories, reliable, less reliable and unreliable (including no use). Long-acting reversible contraceptive (LARC) methods, including intrauterine contraception and implant, hormonal methods and sterilization were classified as reliable; barrier method (condom) was classified as less reliable, as its effectiveness depends on correctness of use; and unreliable methods included those using no or other rare methods of contraception, as well as those where the method was unknown. The study period was very long and included the period before medical methods were introduced. Therefore, for sub-analysis, we divided it into two periods based on the distribution of repeat TOPs overtime. As the share of repeat TOPs plateaued in 2005, the time-period was divided into two periods as 1987–2005 (increasing repeat TOPs) and 2006–2015 (stagnant repeat TOPs).

Statistical analysis

Descriptive analysis was done using cross tabulation to see the differences between the study groups, with a chi-squared test used for the statistical significance. The level of significance was set at <0.01. Univariate and multivariate Cox proportional regression models were used to assess the effect of different factors on the repeat TOPs such as sociodemographic factors, the history of the TOP, including method and gestational age at TOP, and contraception used before the TOP. In the multivariate analysis, all the selected factors were added into the model. Hazard ratios and a 95% confidence interval were calculated. Additionally, Kaplan-Meier curve was used to assess the cumulative risk of first repeat TOP over the study period. A sub-analysis was performed taking into account the period from 2006 to 2015 using the same analysis method as for whole study period. IBM SPSS Statistics version 27 was used for all statistical analysis in this study.

Ethical approval

Permission for the study was obtained from the Finnish Institute for Health and Welfare (THL) in October 2010 (dnro THL/1383/5.05.00/2009), September 2014 (dnro THL/1241/6.02.00/2014) and May 2017 (dnro THL/646/6.02.00/2017).

Results

A total of 193,741 women who had TOP(s) in Finland during 1987–2015 were included in the study. Among them, 78.8% had only one TOP, 15.5% one repeat TOPs and 5.7% had two or more repeat TOPs. The number of repeat TOPs ranged from one to thirteen over the 28-year period. All the factors including demographic and TOP-related characteristics differed significantly between the no repeat TOP and repeat TOP group (Table 1). Younger women, unmarried or single women and women residing in urban areas had higher number of repeat TOPs (Table 1). Repeat TOPs, especially two or more repeat TOPs were markedly higher in recent time-period, 2006–2015 (Table 1).

The median time difference between the TOPs ranged between 2.08 and 3.83 years (Table 2). 17% of repeat TOPs were performed within less than a year of the first TOP, 46% within 1–5 years and 37% after 5 years. In the Kaplan Meier analysis, there was a higher proportion of a single repeat TOP in the shorter time between TOPs among young women.

All the risk factors for repeat TOPs were reduced among women aged 20 years or over compared to the women under 20 (Table 3). Compared to the single or unmarried women, the married or cohabiting women

Table 1
Descriptive characteristics of women having had repeat termination of pregnancy (TOP) in Finland between 1987 and 2015 (n = 193,741).

	No repeat TOP n = 152,681 (%)	One repeat TOP n = 29,971 (%)	Two or more repeat TOPs n = 11 089 (%)	Total n = 193,741 (%)	P-value*
Age					
≤19	23.3	36.3	49.7	26.8	<0.01
20–24	25.7	32.3	32.5	27.1	
25–29	17.5	16.9	12.3	17.1	
30–34	14.5	9.5	4.2	13.1	
35–39	12.1	4.2	1.2	10.2	
≥40	7.0	0.9	0.1	5.6	
Marital status					
Unmarried/single	72.5	84.6	89.6	75.3	<0.01
Married/ cohabiting	26.8	15.1	10.2	24.1	
Unknown	0.1	0.0	0.0	0.1	
Missing	0.5	0.3	0.2	0.5	
Municipality of residence					
Urban	71.2	73.4	73.8	71.7	<0.01
Semi-urban	14.2	13.3	13.3	14.0	
Rural	14.5	13.3	12.9	14.3	
Abroad	0.1	0.0	0.0	0.1	
Parity					
No	56.6	64.1	66.6	58.4	<0.01
Yes	40.8	33.0	30.9	39.0	
Missing	2.6	2.9	2.5	2.6	
Gestational age at TOP					
≤12 weeks	95.8	94.6	93.9	95.5	<0.01
>12 weeks	4.2	5.4	6.1	4.5	
Method					
Surgical	54.7	59.6	63.1	55.9	<0.01
Medical (available since 2000)	40.2	34.0	30.4	38.7	
Others	0.3	0.2	0.3	0.3	
Missing	4.8	6.1	6.2	5.1	
Method of contraception used before TOP					
Reliable	5.4	2.7	1.4	4.8	<0.01
Less reliable	49.9	47.6	45.5	49.3	
Unreliable	44.7	49.6	53.1	45.9	
Indications for TOP					
Social	97.9	97.6	97.3	97.8	<0.01
Medical (women)	0.6	0.3	0.1	0.5	
Ethical	0.0	0.0	0.0	0.1	
Missing	1.5	2.0	2.5	1.6	
Time-period					
1987–2005	65.8	49.4	30.1	61.2	<0.01
2006–2015	34.2	50.6	69.9	38.8	

*P-value < 0.01 in Chi square test.

Table 2
Time interval between repeat termination of pregnancy (TOP) performed in Finland between 1987 and 2015 (n = 41,060).

Time difference between TOPs	Median (IQR), years	<1 year, n = 7,022 (%)	1–5 years, n = 18,872 (%)	>5 years, n = 15,166 (%)
The first and second TOPs	3.83, 1.67–7.50	65.8	70.4	79.5
The second and third TOPs	3.00, 1.33–5.83	22.4	20.6	15.6
The third and fourth TOPs	2.58, 0.92–4.17	7.6	6.1	3.6
The fourth and at least five TOPs	2.08, 0.92–4.17	4.1	2.9	1.3

had a reduced risk of one repeat TOP (adjusted HR 0.80, 95% CI 0.77–0.83) (Table 3). Similar reduced risks were seen for the two, three and four repeat TOPs compared to no repeat TOP. Semi-urban and rural women had decreased risk of repeat TOPs compared to urban women, when comparing one, two, three and four repeat TOPs to no repeat TOP. Moreover, all the adjusted risks of repeat TOPs were higher among parous women than among non-parous women.

Compared to women who had had one or more surgical TOPs, women who had had one or more medical TOPs had a higher risk of one repeat TOP (adjusted HR 1.30, 95% CI 1.26–1.33) (Table 3). Increased adjusted risks were found with additional number of repeat TOPs compared to no repeat TOP. Non-significant risk of one repeat TOP was found among women who had had a TOP after 12 weeks than among those who had the TOP at or before 12 weeks. However, all other adjusted risks for two or more repeat TOPs were lower among the women who had the TOP after 12 weeks than among the women with no repeat TOP. The risks for one and two repeat TOPs were higher among the women using less reliable contraception or unreliable contraception

Table 3
Hazard ratios (HR) and 95 % Confidence intervals for the risk of repeat termination of pregnancy (TOP) among the women having had TOP in Finland during 1987–2015.

	One repeat TOP vs no repeat TOP		Two repeat TOPs vs no repeat TOP		Three repeat TOPs vs no repeat TOP		Four repeat TOPs vs no repeat TOP	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age								
≤19	ref	ref	ref	ref	ref	ref	ref	ref
20–24	0.87 (0.84–0.89)	0.78 (0.76–0.80)	0.68 (0.65–0.72)	0.55 (0.52–0.59)	0.58 (0.53–0.64)	0.41 (0.37–0.46)	0.46 (0.39–0.55)	0.28 (0.23–0.34)
25–29	0.67 (0.65–0.69)	0.55 (0.53–0.58)	0.40 (0.37–0.43)	0.27 (0.25–0.29)	0.26 (0.22–0.30)	0.14 (0.12–0.16)	0.21 (0.16–0.27)	0.09 (0.07–0.12)
30–34	0.46 (0.44–0.48)	0.36 (0.35–0.38)	0.17 (0.16–0.19)	0.10 (0.09–0.12)	0.08 (0.06–0.11)	0.04 (0.03–0.05)	0.04 (0.22–0.07)	0.01 (0.01–0.03)
35–39	0.25 (0.23–0.26)	0.19 (0.18–0.20)	0.06 (0.05–0.08)	0.03 (0.03–0.04)	0.01 (0.01–0.03)	0.01 (0.000–0.01)	0.00 (0.00–0.03)	0.00 (0.00–0.01)
≥40	0.09 (0.07–0.09)	0.07 (0.06–0.07)	0.01 (0.01–0.02)	0.01 (0.00–0.01)	0.00	0.00	0.00	0.00
Marital status								
Unmarried/single	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Married/cohabiting	0.53 (0.52–0.55)	0.80 (0.77–0.83)	0.35 (0.32–0.37)	0.74 (0.68–0.81)	0.27 (0.23–0.31)	0.68 (0.57–0.81)	0.24 (0.18–0.31)	0.74 (0.54–1.02)
Municipality of residence								
Urban	ref	ref	ref	ref	ref	ref	ref	ref
Semi-urban	0.87 (0.84–0.90)	0.87 (0.84–0.90)	0.85 (0.80–0.91)	0.82 (0.76–0.87)	0.83 (0.73–0.93)	0.75 (0.65–0.85)	0.72 (0.57–0.91)	0.62 (0.48–0.79)
Rural	0.82 (0.79–0.85)	0.83 (0.80–0.86)	0.77 (0.72–0.82)	0.76 (0.71–0.81)	0.68 (0.60–0.77)	0.62 (0.54–0.71)	0.62 (0.49–0.79)	0.54 (0.42–0.70)
Parity								
No	ref	ref	ref	ref	ref	ref	ref	ref
Yes	0.72 (0.70–0.74)	1.67 (1.61–1.72)	0.61 (0.56–0.64)	2.59 (2.43–2.76)	0.58 (0.53–0.64)	3.63 (3.23–4.08)	0.61 (0.52–0.71)	5.11 (4.15–6.30)
Method								
Surgical	ref	ref	ref	ref	ref	ref	ref	ref
Medical	1.41 (1.37–1.44)	1.30 (1.26–1.33)	1.78 (1.79–1.87)	1.59 (1.51–1.68)	2.10 (1.90–2.32)	1.82 (1.63–2.03)	3.03 (2.54–3.62)	2.54 (2.07–3.17)
Gestational age at the time of TOP								
≤12 weeks	ref	ref	ref	ref	ref	ref	ref	ref
>12 weeks	1.28 (1.22–1.35)	0.97 (0.92–1.03)	1.43 (1.30–1.57)	0.86 (0.77–0.95)	1.65 (1.39–1.95)	0.81 (0.67–0.98)	1.91 (1.44–2.53)	0.69 (0.49–0.96)
Method of contraception before TOP								
Reliable	ref	ref	ref	ref	ref	ref	ref	ref
Less reliable	1.48 (1.38–1.59)	1.14 (1.06–1.23)	2.54 (2.10–3.07)	1.43 (1.18–1.73)	2.45 (1.72–3.49)	1.05 (0.73–1.51)	7.28 (2.33–22.72)	2.87 (0.91–9.04)
Unreliable	1.74 (1.62–1.87)	1.33 (1.23–1.43)	3.28 (2.71–3.96)	1.80 (1.48–2.18)	3.37 (2.37–4.79)	1.39 (0.97–1.99)	12.64 (4.06–39.39)	4.73 (1.51–14.84)

Adjusted for each predictor variables.

before the TOP than for those who used reliable methods. However, the significance was lost for the risk of three and four repeat TOPs.

In the sub-analysis on women having had TOPs in the recent time-period 2006–2015, the adjusted results were similar for the demographic factors and parity, as in the results from whole study period 1987–2015 (Table 4). However, there was a difference with regards to TOP related factors and contraception. No association was seen for the risk of all repeat TOPs compared to no repeat TOP by the TOP method (Table 4). Similarly, a slightly increased risk for one repeat TOP was found among women having had TOP after 12 gestational weeks. Moreover, non-significant risks for two, three and four repeat TOPs were found by the gestational week at TOP. As in the whole period since 1987, increased adjusted risk for one repeat TOP was found among women who used less reliable or unreliable method of contraception compared to women who used reliable contraception method in the recent time-period. However, no significant risk for more than one repeat TOPs was found for the use of contraception (Table 4).

Table 4
Adjusted Hazard ratios (HR) and 95 % Confidence intervals for the risk of repeat termination of pregnancy (TOP) among the women having had TOP in Finland during 2006–2015.

Characteristics	One repeat TOPs vs no repeat TOP	Two repeat TOPs vs no repeat TOP	Three repeat TOPs vs no repeat TOP	Four repeat TOPs vs no repeat TOP
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age				
≤19	ref	ref	ref	ref
20–24	0.70 (0.66–0.74)	0.51 (0.45–0.58)	0.39 (0.29–0.51)	0.30 (0.18–0.50)
25–29	0.48 (0.45–0.52)	0.29 (0.24–0.34)	0.13 (0.09–0.21)	0.16 (0.08–0.31)
30–34	0.36 (0.33–0.340	0.12 (0.07–0.16)	0.10 (0.06–0.17)	0.03 (0.01–0.12)
35–39	0.22 (0.19–0.24)	0.06 (0.04–0.08)	0.05 (0.02–0.10)	0.00
≥40	0.07 (0.05–0.09)	0.01 (0.01–0.04)	0.00	0.00
Marital status				
Unmarried/ single	Ref	Ref	Ref	Ref
Married/ cohabiting	0.88 (0.82–0.94)	0.81 (0.69–0.95)	0.60 (0.41–0.89)	0.88 (0.44–1.75)
Municipality of residence				
Urban	Ref	Ref	Ref	Ref
Semi-urban	0.88 (0.82–0.94)	0.81 (0.69–0.94)	1.12 (0.83–1.51)	0.50 (0.24–1.04)
Rural	0.87 (0.81–0.94)	0.93 (0.79–1.09)	0.91 (0.65–1.29)	0.73 (0.38–1.41)
Parity				
No	Ref	Ref	Ref	Ref
Yes	1.81 (1.71–1.93)	3.02 (2.65–3.44)	4.43 (3.35–5.87)	5.66 (3.43–9.35)
Method of TOP				
Surgical	Ref	Ref	Ref	Ref
Medical	0.99 (0.93–1.06)	1.01 (0.88–1.15)	0.89 (0.68–1.16)	1.18 (0.71–1.97)
Gestational age at the time of TOP				
≤12 weeks	Ref	Ref	Ref	Ref
>12 weeks	1.11 (1.00–1.22)	1.11 (0.89–1.38)	0.98 (0.60–1.61)	0.94 (0.38–2.34)
Contraception before TOP				
Reliable	Ref	Ref	Ref	Ref
Reliable if used correctly	1.49 (1.17–1.90)	1.39 (0.79–2.47)	0.78 (0.29–2.13)	–
No reliable	1.67 (1.31–2.13)	1.66 (0.94–2.95)	0.92 (0.34–2.51)	–

Adjusted for each predictor variables.

Discussion

In this register-based study, 21% of the women who had had a TOP had repeat TOPs. Of those who had repeat TOPs, the proportion of women having one repeat TOP was more than70%. Being older, married, residing in semi-urban or rural areas, and using reliable method of contraception were protective factors for repeat TOP, however, being parous was found to be a risk factor of repeat TOPs. In the sub-analysis considering the time period after 2006, no difference in risk of repeat TOPs was found by the method and gestational weeks at TOP except a slight and marginal risk for one repeat TOP after 12 gestational weeks.

The major strength of this study is the largest dataset for the longer period, covering all the TOPs performed in 1987–2015, using the Finnish Register of Induced Abortions. Our study period was quite long and there could be possibility of changes overtime with regards to repeat TOPs. Therefore, we performed sub-analyses for the most recent time-period 2006–2015. The quality and coverage of the data has been proven high [21,22]. The reliability study done by previous studies has shown that 99 percent of the index TOP information matched with the register data [16,23]. As all the TOPs during the study period were included, selection bias is likely to be minimal. In this study, TOPs performed due to fetal indications were excluded as they differ from other indications and might affect the future pregnancy.

Information on previous TOPs is routinely validated in the Finnish Register of Induced Abortions, but TOPs performed abroad or before 1983 might be underreported. However, the assumption is that there are relatively few such cases, and these are unlikely to affect our results. Socioeconomic status would have been of great interest as a factor likely to influence repeat TOP, but we could not include that in this study. The information was incomplete, with more than50% of data on socioeconomic status missing from the register. As most of the study cohort are young and students, it is difficult to assess their socioeconomic status. The status of their parents or partners would be of interest, unfortunately, this information was also not available in the Register. A recent cross-sectional study from Sweden and a previous study from Finland reported association between low socio-economic status (low education level) and repeat TOPs [24,25]. In contrast, another Finnish study found no association between socioeconomic status and rate of repeat TOPs [16], however, it was reported that smoking was associated with increased risk of repeat TOP. In that study, the socioeconomic status was defined according to the type of occupation, and if no information on occupation was provided, educational level was transformed to socioeconomic status [16]. The difference in definition of socioeconomic status may cause the variation in results. Smoking is strongly associated with socioeconomic status and sometimes it can be used as a proxy [26].

In this study, all demographic and TOP-related characteristics differ significantly between the no repeat TOP and repeat TOPs. Older, married or cohabiting women and rural or semi-urban women had lower risk for repeat TOPs. Consistent with other studies [16,18,19], our study found a decreased risk of repeat TOPs in older women over 20 years old. However, there are several studies which conflict with our results [9,13–15,27]. Similarly, our finding that single or unmarried women had an increased risk of repeat TOPs, is similar to earlier studies [9,18,23]. Younger and unmarried women might have financial problems in having and using contraception, as well as in having a child. They might also think that a child might interfere with their future opportunities [28]. Women residing in semi-urban and rural areas were also seen to have a reduced risk of repeat TOPs in previous studies from

Finland [18,23]. Urban women might seek TOP services more often because of easy accessibility and availability of health services in those areas. There could also be differences in educational level, occupation and income as well as traditional norms between the rural and urban women, that might influence the likelihood of repeat TOP.

Being parous as a risk factor for repeat TOP is one of the other important findings of our study, and consistent with previous studies [15–17,20,27]. Parous women may have already reached their desired family size and seek more repeat TOPs because they do not want to take on another child [29]. It has also been documented in an earlier study that the TOP rate was at its peak at 6–8 months of postpartum, especially among young women and teenagers [30]. This might indicate that contraception use among youth and teenagers was not satisfactory.

In this study including the whole time period from 1987 to 2015, medical TOP was found as a risk factor for repeat TOPs. However, considering the time period after 2006, we found no significant difference in risk of repeat TOP by the TOP method, which corresponds to the result of another earlier study from Finland [23]. The earlier Finnish study also consider the time period after the medical TOP had been introduced. Medical TOPs can partly be carried out outside health facilities since no surgical procedure is required, and women might feel the procedure to be less painful, which could be possible reasons that women undergoing medical TOP might seek more TOPs. However, it could not be ignored that surgical TOP was more common in the early period of our study before 2006 and after that almost surgical TOPs have been replaced by medical TOP. In this study, no significant risk of repeat TOPs was found after a TOP performed above 12th gestational weeks, which is in line with a recent study [20]. In contrast with this result, however, a Finnish study [18] found the second trimester TOP was associated with repeat TOPs and also with repeat TOPs during the second trimester.

Women using reliable methods of contraception such as LARC, hormonal methods and sterilization showed reduced risk of repeat TOPs than those using less reliable and unreliable methods. Much earlier evidence supports our findings [16,17,19,20]. Intrauterine contraception after the TOP showed high efficacy in reducing the risk of repeat TOPs [16,23,31]. Further, previous studies reported reduced TOP rate among women using LARC methods than those using no LARC methods [32,33]. However, in a previous randomized study, specialist contraceptive counselling and provision after TOP increased the initial uptake of LARC methods but did not show any effect on repeat TOPs [34] Further, it is possible that women using the LARC method might discontinue the method. A recent study [35] showed a greater discontinuation among women using implants and copper intrauterine device than among those using levonorgestrel-releasing intrauterine system. In addition, the immediate initiation of any contraceptive after a TOP, rather than not using any method, may possibly reduce the need for repeat TOPs [16,27].

Conclusion

Older age, being married, rural or semi-urban residence and using reliable contraception were found to be protective factors for repeat TOPs whereas, parous women had higher risk for repeat TOPs. Information regarding repeat TOPs and factors influencing repeat TOPs should be included in sexual and reproductive health education in school health education. Proper counselling at the time of a TOP and the immediate initiation of reliable contraception should be significant in assisting women to avoid the need of subsequent TOPs. Provision of contraception among the youth by making it more accessible and available at low cost or free of charge is essential to reduce repeat TOPs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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