ADVANCED MATERNAL AGE AND PLACENTA PREVIA FOR WOMEN GIVING BIRTH IN FINLAND; A REGISTER-BASED COHORT STUDY

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Master's thesis
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May 2017
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Increasing maternal age at the time of delivery and the prevalence of placenta previa provided more implications in practice. Thus, the aim of this study was to assess the association of Advanced Maternal Age (AMA) with placenta previa and to explore the effect of AMA on maternal and neonatal outcomes of placenta previa.

This study was a register-based cohort study, using data of three Finnish health registries from 2004 to 2008, including information of 283,324 women and their newborns. The association between AMA and placenta previa was modelled using a backwards, stepwise logistic regression. Multivariable logistic regression modelling was used to assess the effect of maternal age 35 years or older on maternal and neonatal outcomes of placenta previa. The main outcome measures were blood transfusion, placental abruption, preterm birth <37 weeks, Neonatal Intensive Care Unit (NICU) admission, low birth weight <2,500 g and low Apgar score at 5 minutes.

A total of 283,324 deliveries, of which 714 (0.3%) were complicated by placenta previa. AMA was an independent risk factor for placenta previa, Adjusted Odds Ratio (AOR) 1.54; 95% Confidence Interval (CI) (1.30-1.83). Adverse maternal and neonatal outcomes generally increased in women with placenta previa, with different patterns across age groups. By considering women without placenta previa as reference groups, the AOR 95% CI in AMA and young women with previa were 7.3 (5.0-10.6) and 6.8 (5.2-8.9) in blood transfusion, 11.3 (5.4-23.3) and 10.9 (6.1-19.6) in placental abruption. In neonatal outcomes the AOR and 95% CI in AMA and young women with placenta previa were 8.8 (6.6-11.6) and 11.7 (9.7-14.1) in preterm birth, 4.0 (3.0-5.3) and 4.9 (4.1-5.9) in NICU admission, 4.0 (2.8-5.7) and 5.9 (4.7-7.4) in low birth weight, 2.7 (1.5-4.9) and 3.3 (2.2-5.0) in low Apgar score at 5 minutes.

The results demonstrated that AMA was an independent risk factor for placenta previa. AMA women with placenta previa had slightly higher adjusted risks of blood transfusion and placental abruption than younger women with placenta previa, but not greater risks of neonatal outcomes.
ACKNOWLEDGMENTS

The present study was carried out at Department of Public Health, Faculty of Health Sciences University of Eastern Finland. The second aim of this thesis was based on the manuscript with the topic of ‘The effect of advanced maternal age on placenta previa outcomes: a register-based cohort study’ which is currently under review in a journal.

I would like to thank Professor Katri Vehviläinen-Julkunen, PhD, for supervising my thesis and giving guidance. I would like to thank Professor Tomi Pekka-Tumainen, MD, PhD for supervising me and giving continuous support. I would like to thank Professor Seppo Heinonen, MD, PhD, for his time, knowledge and guidance. I would like to thank Reeta Lamminpää, PhD, for giving all help and prompt answers to my questions. I would like to thank Ari Voutilainen, PhD, for his kind assistance in plotting figures and giving statistical guidance. I would like to thank The National Institute for Health and Welfare for giving me the possibility to use register-based data. I owe my deepest gratitude to all of them for their support.

Kuopio
May 2017

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1 ABBREVIATIONS

AMA  Advanced Maternal Age
AOR  Adjusted Odds Ratio
ART  Assisted Reproductive Technology
CI   Confidence Interval
ICD  International Classification of Diseases
IUI  Intrauterine Insemination
IVF  In-Vitro Fertilization
LBW  Low Birth Weight
MBR  Medical Birth Register
NICU Neonatal Intensive Care Unit
SGA  Small for Gestational Age
THL  The National Institute for Health and Welfare
US   United States
2 INTRODUCTION

Postponement of motherhood has become the main characteristic of fertility patterns in many developed countries (Mathews & Hamilton 2009). In the last decades, the trend toward delaying motherhood and the shift in age demographic were so prominent that Goldstein and associates (2009) used the term ‘postponement transition’ as a change from the younger to the older age of motherhood. In Finland, the average age of women at first child increased from 26.5 in 1987 to 28.8 in 2015 (Klemetti et al. 2016, THL 2017). The process of postponement transition has negatively affected the demographic situation and overall fertility rates in many developed countries (Billari & Kohler 2004). Although, women are aware of associated risks of postponing motherhood, they postpone childbearing for many reasons, ranging from individual, family and social to national and international factors (Maheshwari et al. 2008, Fagbamigbe & Idemudia 2016). Advanced Maternal Age (AMA) is mainly determined as maternal age more than 35 and there is a growing body of evidence that AMA is associated with adverse pregnancy outcomes (Usta & Nassar 2008, Bayrampour & Heaman 2010, Kenny et al. 2013).

The prevalence of placenta previa was estimated to be 5.2 per 1000 pregnancies (Cresswell et al. 2013). Placenta previa is an obstetric complication in which the internal cervical os is partially or completely covered with placental and is a leading cause of abnormal antepartum bleeding (Cunningham et al. 2010). The risk of having placenta previa in pregnancies is increasing as a result of changing trends in risk factors such as increased rates of Caesarean section and introduction of In-Vitro Fertilization (IVF) in fertility treatment ((Nørgaard et al. 2012). Studies indicated that placenta previa is significantly associated with adverse maternal and neonatal outcomes (Crane et al. 2000, Rosenberg et al. 2011, Mastrolia et al. 2016).

Despite a large volume of literatures in the area of advanced prenatal outcomes of AMA and placenta previa, the association between AMA and the risk of placenta previa was not consistent across studies. Furthermore, we hypnotized that the effect of poor placenta bed in placenta previa compound with uteroplacental under perfusion in AMA may worsen pregnancy outcomes. However, evidence supporting the effect of individual-level risk factors such as AMA on placenta previa outcomes is lacking. Thus, population-based data were used to assess the association of AMA with placenta previa and to explore the effect of AMA on perinatal outcomes of placenta previa, in terms of magnitude of the adverse outcomes from younger women with placenta previa.
3 LITERATURE REVIEW

3.1 Advanced Maternal Age

3.1.1 Definition of Advanced Maternal Age (AMA)

It has always been arguments about the optimal timing to be a mother, but there is no consensus on the exact definition of AMA. In social sciences, AMA is considered as the normative acceptability of older parenthood in the society (Boivin et al. 2009). In the majority of European countries, the age at which is considered too late to get pregnant is over the age of 40 (Mills et al. 2011). From a medical point of view, AMA is usually defined based on pregnancy outcomes that affect the wellbeing of mothers. In today's world, postponing motherhood is more acceptable and sometimes it is considered to be beneficial for women, because of bringing sociological advantages over biological disadvantages (Stein & Susser 2000). From a social perspective, older mothers have more stable sources of income, higher levels of education and more life experience (Nilsen et al. 2012). From a medical perspective, AMA women have more pregnancy-related complications than younger women (Laopaiboon et al. 2014).

In assessing the effect of maternal age on pregnancy outcomes, it is necessary to draw a boundary between the low-risk and high-risk pregnancies. Studies reported different boundaries for defining the adverse effect of maternal age on pregnancy outcomes. However, AMA is commonly defined as maternal age 35 or older and majority of studies used this cut-off age to evaluate adverse pregnancy outcomes (Usta & Nassar 2008, Mills & Lavender 2010).

Some studies considered the cut-off age of 30 to assess whether there was an increased risk before the cut of age of 35 years, while in other studies a cut-off age was considered more than 40 or 45 (Blomberg et al. 2014, Grotegut et al. 2014, Waldenström et al. 2014). The study of Klemetti and associates (2016) reported precise threshold-ages for adverse pregnancy outcomes by considering maternal age as a continuous variable, without defining any specific boundaries. However, the study of Cleary-Goldman and associates (2005) suggested that maternal age has a continuum effect rather than a threshold effect.
The exact definition of AMA is hard to define, because the risk of unfavorable pregnancy outcomes may occur earlier or later than a 35 years cut-off age (Lamminpää 2015). However, this thesis may contribute more to the exact definition of AMA by focusing on the medical aspects of age-related complications.

3.1.2 Postponing childbirth

Postponement of childbearing has been linked to the demographic transition in many developed countries (Lesthaeghe & Neels 2002). The phenomenon of demographic transition was defined as the transition from high birth to low birth rates and begun in the beginning of the 19th century in Europe, known as ‘the first demographic transition’. The first transition was mainly influenced by concerns for family and offspring, characterized by urbanization, industrialization and secularization (Van de Kaa 1987, Lesthaeghe 2014). In the first transition, economic utilization of children was reduced and parents had to invest more on children to give them a better chance of future life. At the same time, the influence of churches was reduced by secularization and use of birth control device increased (Van de Kaa 1987). The second transition happened in the 1960s and moved Europeans from marriage and parenthood toward individualism with increasing rates of divorce and premarital cohabitation in postindustrial societies (Bianchi 2014). During this period, men and women tended to have a decent income and a deliberate choice of bringing a child for women meant to leave their job. Beyond economic reasons, social and cultural factors played a substantial role in postponing marriage and parenthood in postindustrial societies. The second transition emphasized on the fact that how changes in values and attitudes can play roles in postponing parenthood, while in the first transition the main reason for demographic transition was value of children (Bianchi 2014).

In recent societies, the increase in the mean maternal age at the time of delivery has become an important characteristic of women in many developed and some developing countries. The recent worldwide trends in postponing pregnancy and decreasing fertility rates were so tangible that some studies reported AMA as a public health issue and French High Council for Population and Family recommended to consider AMA as a public health agenda (Lemoine & Ravitsky 2015). The shift in average maternal age toward later motherhood has been reported in many developed countries. The mean maternal age at delivery of the first child increased almost 5 years in Denmark from
1978 to 2007 (Nørgaard et al. 2012). The rise in maternal age has been observed in the United States (US); the mean maternal age increased in all race and Hispanic origin groups, from 24.9 in 2000 to 26.3 in 2014 (Mathews & Hamilton 2016). Canada had an almost 3-fold increase in the proportion of AMA women from 1987 to 2005 (Lemoine & Ravitsky 2015). In Australia, the median age of mothers increased from 25.4 years in 1971 to 29.3 years in 2013 (Allison et al. 2016). On the other hand, similar trends have been observed in some developing countries. In Iran, many factors have contributed to decline in fertility rates from 6.9 in 1980 to 1.6 in 2011, of which 31% was due to the postponement of marriage among young adults (Saadat et al. 2010, Erfani 2014).

3.1.3 Factors associated with postponing childbirth

The underlying reasons for postponing childbearing are divers in different time periods. In the first transition, economic factors and changes in child labour attitudes were the main reasons for postponing parenthood (Van de Kaa 1987). Given the recent trends in childbearing age, the tendency towards postponing childbirth results from a myriad of factors, ranging from individual, family and social factors to national and international factors (Fagbamigbe & Idemudia 2016). In recent decades, social advance toward women empowerment provided women with an opportunity to pursue education and career goals before having a family (Hadfield 2007). Acquiring higher levels of education usually is time consuming and balancing the role of motherhood with educational attainment is hard to achieve. Therefore, women prefer to postpone motherhood to the later time. Furthermore, well-educated women tend to have serious careers which need more time, responsibility and autonomy (Mills et al. 2011). Thus, women prefer to postpone motherhood until the time they reach stability in their career.

Another underlying reason for delaying childbearing is that nowadays women have a greater control over their pregnancy, thanks to widespread use of contraceptives and the possibility of legal abortion in some countries (Bailey 2006). Therefore, women are able to manipulate the timing of reproduction and allocate less time to the maternal role. Additionally, the introduction of Assisted Reproductive Technology (ART) in the 1970s gave the notion that pregnancy is possible at even older age, without knowing the fact that the success rate of ART is highly related to the age of mothers (Simpson 1998, Leridon 2004). Moreover, the transition to motherhood can be inhibited by physical wellbeing, emotional conditions, stressful environment and lack of
knowledge (Meleis et al. 2000). On the other hand, in some situations postponing motherhood is not an individual choice and is mainly guided by external factors. Study of Abu Heija and associates (2000) reported that women in Jordan continue to bear children until the end of childbearing years, because of social and religious reasons. Housing and economic uncertainly and lack of family support policies as well as a departure from traditional values, norm and beliefs are another determinants of postponing childbearing (Mills et al. 2011).

### 3.1.4 Postponing childbirth in Finland

Like other developed countries, in Finland, there is a tendency toward postponement of childbearing and Finnish birth cohorts confirmed this trend. In Finland, the proportion of primiparous mothers aged 40 or older has increased from 12% in 1987 to 20% in 2010 (Klemetti et al. 2013). Finnish mothers had the mean maternal age of 26.5 in 1987 and 28.8 in 2015, with an almost 2-year increased (Klemetti et al. 2016, THL 2017). The results of a comparative research showed that irrespective of all similarities in fertility patterns among the Nordic countries, Finnish women had the highest mean age and Norwegian women had the lowest mean age at birth. In Finnish women, the process of postponement of childbearing started in the 1945−49 cohort, sooner than the other Nordic countries, but this postponement transition has not ground to a halt (Andersson et al. 2009).

In Nordic countries gender equality policies encouraged women to participate actively in the society. Consequently, the proportion of women with university degrees has substantially increased and among all Nordic countries, Finland has had the highest proportion of women with higher education. This preference of Finnish women in taking educational opportunities was linked to the highest median age of Finnish mothers at the time of delivery among Nordic countries. However, higher level of education in Finnish mothers was not associated with a lower number of children (Andersson et al. 2009). This effect may be modified by the Finnish family policy and paid parental leave that try to keep the birth over the replacement level of developed countries so that women preferred to take the advantages of unemployment for a while (Vikat 2004, Eurostat 2017). Thus, in Finnish mother, AMA is associated with higher levels of education, later transition to motherhood, but not the lower number of children. This inverse relationship between levels of education and the timing of the first child has been documented in another study (Martin 2000).
From a biological perspective, older women tend to marry with older men and this can contribute to subfertility or in fecundability. Although the ability to conceive is less affected by age in men, in AMA women the biological ability to conceive decreases with advancing age (Dunson et al. 2002). Thus, postponing pregnancy to the older age may affect to some extent, the total fertility rate in Finland and it has contributed to the rate of fertility below the recommended replacement level for developed countries (Regushevskaya et al. 2013). Along with increase in maternal age and decline in fertility rate, the use of ART has increased in Finland and 4.2 of newborns were artificially convicted in 2014 (THL 2015a). However, use of ART cannot entirely compensate the decline in fertility by age (Schmidt et al. 2012).

One study in the US reported that AMA is associated with a higher risk of maternal mortality, but recent advances in technology and medical care has ameliorated the risk of maternal mortality (Buehler et al. 1986). However, Klemettie and associates (2013) reported that despite all changes and advances in maternity care in Finland, older mothers use more antenatal services than the younger counterpart, which stems from the fact that AMA women and their infants have more health problems. Although, AMA is associated with more use of antenatal services and higher rates of interventions, these associations cannot be entirely explained by higher rates of pregnancy complications in this age group. One study in the United Kingdom reported that, higher rates of interventions in older women reflect AMA as a real phenomenon and it cannot be entirely explained by more obstetric complications (Bell et al. 2001).

### 3.1.5 The causal effect of AMA and adverse pregnancy outcomes

Numerous studies have reported that AMA is associated with multiple adverse pregnancy outcomes. Maternal and neonatal complications, including chromosomal abnormalities, congenital anomalies, low birth weight, preterm birth, diabetes, high blood pressure, preeclampsia, breech presentation, operative vaginal delivery, emergency Caesarean section, postpartum haemorrhage, birth weight below the 5th percentile, stillbirth and placenta previa (Jolly et al. 2000, Delbaere et al. 2007, Flenady et al. 2011, Laopaiboon et al. 2014). A study of 34,695 pregnant women with singleton pregnancy found higher rates of pre-existing medical conditions such as diabetes and high blood pressure in advanced maternal age women in compared to women aged 25 to 29 years (Ludford et al. 2012). Grotegut and associates (2014) reported that the number of women giving birth in 45 years and more is increasing and found that these women had increased risks of maternal
death. In addition to that aggregated results of 38 countries revealed that maternal mortality has a "J" shaped curve and the risk increased after age 30 (Blanc et al. 2013). Therefore, the results of these studies indicated that AMA contributes to multiple adverse effects rather than a single effect on pregnancy. In other words, AMA not only increases the risk of age-related complications such as diabetes or hypertensions, it is associated with higher risks of many other maternal and neonatal adverse outcomes.

Studies used different effect measures to evaluate the association of AMA with adverse pregnancy outcomes, but most of the studies reported that there is a strong association between AMA and pregnancy outcomes. Even after controlling for potential confounding factors, the strength of association between AMA and pregnancy outcomes persists (Cleary-Goldman et al. 2005, Biro et al. 2012). The existence of statistically significant associations in the majority of studies illustrates more on the importance of AMA as a risk factor for many pregnancy complications and indicates that AMA quantitatively and clinically is connected to adverse outcomes in pregnancies.

Additionally, the effect of AMA on pregnancy outcomes may be worsened by the effect of different risk factors. For example, based on “weathering” hypothesis, the risk of preterm birth in older African Americans was greater than white Americans mothers (Holzman et al. 2009). According to “weathering” hypothesis, the effect of health inequality coupled with AMA, widened the gap between adverse pregnancy outcomes in African Americans and white Americans. Another study reported that the adverse effect of smoking on the risk of preterm birth intensifies in AMA women. It means that older mothers are more affected by the detrimental effect of smoking than younger mothers (Boneillie 2001). Thus, in many circumstances, older women had more unfavorable pregnancy outcomes than younger counterparts and various factors such as health inequity and smoking may lead to increased risks of unfavorable pregnancy outcomes.

In some studies, maternal age was categorized in different categories to assess different levels of exposure of risk factor on pregnancy outcomes. In the study of Jolly and associates (2000) was reported that the odds of having gestational diabetes, breech presentation, operative vaginal delivery, elective and emergency Caesarean sections, postpartum haemorrhage, preterm birth and stillbirth, in mothers aged over 40 was stronger that mothers aged 35-40. Therefore, the category of women aged over 40 had greater risks of developing adverse pregnancy outcomes than the category of 35-40. This cumulative adverse effect of maternal age on pregnancy outcomes emphasizes more on the causal relation of AMA and adverse pregnancy outcomes.
Studies reported a number of biological plausible mechanisms for the association of AMA and pregnancy outcomes. It has been reported that the risk of adverse neonatal outcomes increases in AMA women because of increasing in the risk of congenital malformations and chromosomal anomalies, but after controlling for the confounding effect of congenital malformations, the magnitude of associations was still exists (Luke & Brown 2007). In fact, maternal age can affect the uterine blood flow and with advancing age, uterine blood flow decreases. Large uterine infarcts and uteroplacental under perfusion were observed in AMA women (Pirhonen et al. 2005). Additionally, a blinded invitro study showed that spontaneous myometrial contractility was independently associated with maternal age, AMA may affect gap junction or ion channel expression as well as control of electrical activity in the myometrium. Thus, impairment of myometrial contractility may be a possible reason for higher risks of Caesarean section, prolonged labour and emergency Caesarean section in AMA women (Smith et al. 2008). Furthermore, the number of oxytocin receptor decreases with advancing age; consequently a higher dose of oxytocin is needed to prevent postpartum haemorrhage in AMA women (Adasen et al. 1993). Based on these studies, less efficient uterus in AMA women is expected and these theories emphasized more on the fact that the association of AMA and adverse pregnancy outcomes is plausible.

3.1.6 AMA and placenta previa

As reported in studies, AMA is associated with a wide range of adverse pregnancy outcomes in this regard uteroplacental insufficiency and placental dysfunctions were the basis of many adverse pregnancy outcomes in AMA women (Miller 2005). One study reported that AMA was associated with heavier placenta weight and that can be an explanatory reason for many adverse pregnancy outcomes (Haavaldsen et al. 2011). Therefore, according to these studies, there was a clear effect of aging on placenta functions. However, the result in previous studies about the effect of AMA on placenta previa was inconsistent and studies with small sample size could not prove this association (Wolff et al.1997, Favilli et al. 2012).

In several studies, it was unclear whether advanced maternal age was an independent risk factor for placenta previa or was just demonstrative of more opportunity for adverse pregnancy outcomes (Joseph et al. 2005, Carolan et al. 2013). In the study of Biro and associates (2012), AMA was independently associated with placenta previa with the AOR of 2.2. However, the effect of ART was not considered as a potential confounding factor.
Based on the current evidence, the association of AMA with placenta previa was reported differently. In some studies, the strength of association was strong, weak or in other studies no associations were found. Thus, the findings of the current study will reinforce the association of placenta previa with advancing maternal age.

3.2 Placenta previa

3.2.1 General aspects

Placenta previa is an obstetric complication in which the internal cervical os is partially or completely covered by placenta, characterized by painless vaginal bleeding (Oyelese & Smulian 2006). Based on the position of placenta, four degrees of placenta previa have been described, total, partial and marginal placenta previa as well as low-lying placenta. Although the internal cervical os is not covered by low-lying placenta, a low-lying placenta may change to a partial placenta previa in cervical dilatation (Cunningham et al. 2010).

The frequency of placenta previa decreases with gestational age and only 19% of patients, who were diagnosed with placenta previa at second trimester, have the condition at 26-30 weeks (Taipale et al. 1998). King (1973) used the term 'placenta migration' for the situation in which the position of placenta is being renewed with advancing gestational age. Whereas, according to trophotropism hypothesis, placenta develops in the direction of better vascularized positions (Benirschke & Kaufmann 1990). Another explained theory is that apparent placenta migration is due to growth of lower segment (Oyelese & Smulian 2006). The possibility of migration of anterior placenta previa and low-lying placenta is more than posterior placenta previa (Cho et al. 2008).

3.2.2 Etiology and risk factors of placenta previa

The incidence of placenta previa was reported to be 0.3–0.5% and the magnitude of the excess risk for placenta previa varied in different settings due to ethnic differences among populations (Iyasu et al. 1993, Cresswell et al. 2013). The prevalence of placenta previa was common in Asian studies (12.2 per 1000) and rare in Sub-Saharan Africa (2.7 per 1000). This wide disparity in the prevalence of placenta previa can be explained by different trends in risk factors (Ahmed et al. 2016). For example, the incidence of placenta previa was high in populations with higher rates of Caesarean section (Silver et al. 2006).
The exact cause of placenta previa is not completely understood. However, several risk factors are associated with placenta previa such as parity and multiple pregnancies. Ananth and associates (1996a) reported that after adjusting for maternal age, the risk of placenta previa was higher in women at parity 3 or higher than nulliparous women. In addition to that, the frequency of placenta previa was 40% among multiple pregnancies in comparison to singleton pregnancies (Ananth et al. 2003a). The possible explanatory reason for the association of multiple pregnancy with placenta previa is that in the US along with increasing in the proportion of AMA women, the use of ART has substantially increased so that twin pregnancies are more expected. Since placenta is larger in twin pregnancies than singleton pregnancies, the possibility of having placenta previa is greater in multiple pregnancies (Strong & Brar 1989).

The rate of Caesarean section in Finland is not high and it has been reported to be 16%, but studies reported that Caesarean section both contributes and associates with placenta previa (EURO-PERISTAT 2013, Räisänen et al. 2014). On the one hand, previous caesarean section is an independent risk factor for placenta previa. On the other hand, the likelihood of giving birth by Caesarean section was higher in nulliparous women with placenta previa. In a meta-analysis with 37 included studies was reported that after Caesarean delivery at first birth, the risk of placenta previa increased by almost 2-fold in the following pregnancy (Gurol-Urganci et al. 2011). In another study, not only the association between Caesarean section and subsequent placenta previa was assessed, but also the relationship between additional Caesarean section and placenta previa was evaluated. The results indicated that after three or more Caesarean sections the risk of placenta previa increased more than 3-fold (Gilliam et al. 2002). Moreover, the impact of elective abortion on subsequent pregnancy has widely discussed. One of the adverse effects of elective abortion, especially multiple sharp curettage abortion method is a higher risk of placenta previa in subsequent pregnancies. Furthermore, multiple prior abortions and abortions complicated by infection are associated with an increased risk of placenta previa (Johnson et al. 2003).

From another point of view, the majority of women who underwent ART are AMA women and after controlling for the effect of age, ART was an independent risk factor for placenta previa (Johnston et al. 2015). The risk of placenta previa was 6-fold higher in pregnancies followed assisted reproduction than naturally conceived pregnancies (Romundstad et al. 2006a). A population based cohort study, comprising data of ART deliveries in Finland, Norway, Sweden and Denmark from 1982 to 2007 reported that placenta previa was strongly associated with ART
and the risk of placenta previa in ART pregnancies increased with advancing age till the age of 30, while the risk of placenta previa in AMA women did not differ between ART and naturally conceived pregnancies (Wennberg et al. 2016). A plausible reason for the association of ART with placenta previa is that mechanical procedure of transferring the embryo in ART may cause secretion of prostaglandin and more contractions. Thus, implantation in the lower uterine segment was more common in pregnancies conceived by ART (Romundstad et al. 2006).

Uterine scarring from previous Caesarean sections, previous curettages and in general previous surgeries on uterus contribute to the abnormal implementation of placenta. These situations lead to suboptimal endometrial tissue, thinner myometrium, poor blood perfusion and less suitable place of anterior uterine for placenta implantation. Therefore, placenta is implemented in the healthier segments of the lower uterine (Gibbs & Danforth 2008).

Some studies reported that smoking is an independent risk factor for placenta previa (Ananth et al. 1996b, Salihu et al. 2003), while in other studies there was no association between smoking and placenta previa (Rosenberg et al. 2011, Räisänen et al. 2014). One possible explanation, for the positive association is that Carbone monoxide hypoxemia due to smoking contribute to compensatory placenta hypertrophy. Thus, there is more possibility that placenta covers the internal os of cervix. In smoking women with placenta previa, fibrinoid changes in maternal decidual arteries, fibrotic peripheral villi, villous hyperplasia, and marginal placental necrosis were reported for microscopic and macroscopic abnormalities of placenta (Williams et al. 1991).

Studies postulated that the risk of placenta previa has increased in recent decades. The rising rates of placenta previa emanate mainly from changing risk profiles in women such as increasing in the rates of Caesarean section and the mean of maternal age (Ahmed et al. 2016). Additionally, the rise in the incidence of placenta previa was parallel with the growing use of ARTs. Study of Nørgaard and associates (2012) reported that the introduction of In-Vitro Fertilization (IVF) treatment since 1980, as a strong risk factor for placenta previa, was one of the contributing factors for increasing placenta previa rate in Denmark.

### 3.2.3 Effect of placenta previa on maternal outcomes

The rising rates of placenta previa may add to the risks of various potential maternal complications related to placenta previa. Women with placenta previa are exposed to more pregnancy complications such as placental abruption, placenta accreta, postpartum anaemia, fetomaternal
haemorrhage, peripartum hysterectomy due to uncontrolled bleeding, postpartum haemorrhage, second trimester bleeding, mal presentation and delayed maternal and infant discharge from the hospital (Crane et al. 2000, Sheiner et al. 2001, Rubod et al. 2007, Rosenberg et al. 2011).

In the modern practice, in spite of all improvements in bleeding management during pregnancy and availability of blood transfusion, haemorrhage is still a leading cause of maternal mortality (Berg et al. 2010). More than half of pregnancies complicated by placenta previa experienced antepartum haemorrhage and women with placenta previa and prior uterine scar may experience higher risks of bleeding (Fan et al. 2017). In antepartum, placenta detachment sooner than deliver or placental abruption may happen in women with placenta previa and cause massive bleeding that can jeopardize the infant's life or contribute to maternal coagulopathy (Tikkanen et al. 2006, Gibbs & Danforth 2008). In intrapartum, severe bleeding in pregnancies complicated by placenta previa may result from abnormal placental attachments and contribute to emergency Caesarean section and peripartum hysterectomy (Wong 2011). Suboptimal placenta place in the lower segment is responsible for this firm attachment of placenta (Moretti et al. 2014). In addition to that, the results of 50 placental bed biopsies of placenta previa cases showed trophoblastic cell invasion of myometrial spiral arterioles was higher in placenta previa cases, which is the characteristic of placenta previa with some degrees of placenta accreta (Biswas et al. 1999). In postpartum, the lower segment of the uterus has less ability to contract than urine body so that abnormal bleeding is expected after birth (Albayrak et al. 2011). From another point of view, higher frequency of abnormal presentation, such as breech presentation and transverse lie, was reported in pregnancies complicated by placenta previa (Seffah 1999, Bin et al. 2016). Placenta previa combined with transverse lie are associated with maternal morbidities such as abnormal postpartum bleeding (Kramer et al. 2011). Therefore, repeated bleeding in women with placenta during antepartum as well as massive bleeding in intrapartum and postpartum may increase the risk of anaemia and in women with anaemia, more adverse effects are expected in the postpartum period such as depression (Bergmann et al. 2010).

Pregnancies complicated by placenta previa have higher risks of antepartum, intrapartum and postpartum hemorrhage. Bleeding and recurrent hospitalization impose higher emotional stress on women (Katz 2001). Additionally, in women with diagnosed placenta previa costs related to hospitalization, repeated ultrasound, higher risks of emergency Caesarean and longer stay in
hospital due to Caesarean section associated with a financial burden on patients and healthcare systems (Eichelberger et al. 2011).

3.2.4 Effete of placenta previe on neonatal outcomes.
Suboptimal place of placenta in the lower uterine not only increases the risk of maternal complications, but also increases neonatal adverse outcomes, including preterm birth, neonatal death, perinatal death, respiratory distress syndrome, anaemia, congenital malformation. (Crane et al. 1999, Lal & Hibbard 2015, Vahanian et al. 2015).

Preterm delivery is the major concern in women with placenta previa and the main focus in placenta previa management is to reduce preterm birth and related consequences. Study of Erez and associates (2012) showed that women with placenta previa who delivered before 37 weeks of gestation or especially those who delivered before 34 weeks of gestation, had higher risks of delivering preterm in subsequent pregnancy regardless of the position of the placenta. Thus, by delivering infants as close as possible to the term, prematurity and related comorbidities can be reduced (Oyelese & Smulian 2006). In a population-based study was reported that pregnancies complicated by placenta previa experienced a 3-fold increase in the risk of neonatal mortality than pregnancies without placenta previa and this association was mediated by preterm birth rather than Small for Gestational Age (SGA) (Salihu et al. 2003). However, according to the results of Nørgaard and colleagues (2012), even in term pregnancy high risk of low Apgar score of ≤7 at 5 minutes and NICU admission was expected in pregnancy with placenta previa. Additionally, in the study Ananth and associates (2003b) infants delivered at 36 weeks of gestation had lower rates of neonatal death than pregnancies without placenta previa. This can partly be explained by the reason that women with placenta previa received more steroid for infant lung maturity.

In women with placenta previa infants have 210 g lower mean birth weight than pregnancies without placenta previa and prematurity mediate the association of placenta previa with low birth weight, but not with SGA (Ananth et al. 2001, Walfisch and Sheiner 2016). Additionally, Räisänen and associates (2014) reported that after controlling for possible confounding factors in multiparous women, placenta previa was a risk factor for SGA, but SGA was not associated with placenta previa in nulliparous women. Although the association of placenta previa with SGA is due to placenta insufficiency, Happer and associates (2010) reported that placenta previa was not always identified with uteroplacental insufficiently and in their study, placenta previa was not
associated with birth weight less than 15\textsuperscript{th} percentile and less than 10\textsuperscript{th} percentile. Moreover, high risks of preterm birth, low birth weight, SGA and low Apgar score in pregnancies with placenta previa, increased the risk of an infant being admitted in NICU (Vahanian et al. 2015).

3.2.5 Effect of risk factors on placenta previa outcomes
Most research has focused on adverse maternal and neonatal outcomes of placenta previa and the impact of other risk factors on the outcome of placenta previa has rarely assessed. Clinical outcomes of placenta previa vary from woman to another woman and they cannot be entirely anticipated. However, some risk factors may worsen the adverse outcomes of placenta previa. For example, study of Silver and associates (2006) showed that prior Caesarean sections coupled with placenta previa added to the risk of placenta accreta. Additionally the likelihood that placenta previa remains previa till term is higher in women with prior Caesarean sections due to previous damage to the uterine (Dashe et al. 2002). Moreover, women with placenta previa and prior Caesarean sections had higher risks of massive bleeding during Caesarean section (Hasegawa et al. 2009). These examples illustrate that a risk factor such as prior Caesarean section can magnify the adverse outcomes of placenta previa.

Nowadays, women are postponing pregnancy for many reasons and it is likely that AMA is associated with adverse pregnancy outcomes, because of uteroplacental insufficiency and the effect of aging on the vessels. It is conceivable that the combination of AMA with suboptimal place of placenta in placenta previa may worsen maternal and neonatal outcomes. However, the extent to which AMA is associated with adverse outcomes of placenta previa has not been researched. This thesis attempts to evaluate the potential negative effects of AMA on maternal and neonatal outcomes of placenta previa.

3.3 Register-based study
3.3.1 Register-based data in pregnancy research
There are practical questions and concerns for couples regarding adverse pregnancy outcomes and sometimes providing answers and giving assurance require conducting epidemiological research. In Finland, the first perinatal studies were based on three large birth cohorts, but usually cohort studies are expensive and time-consuming (Gissler et al. 1997). Nowadays, many countries have
introduced birth registries as a valuable source of epidemiological studies of this kind, with coverage of 97% to 100% of the population (EURO-PERISTAT 2004). Existing register-based data generate important hypotheses to start research. Retrospective evaluation of birth registers has been used to evaluate the effect of social characteristic on birth outcomes and the effect of prenatal period on pregnancy outcomes. Furthermore, many complications have a long latency period and availability of data enables researchers to evaluate the association between stressors in pregnancies and increased risk of diseases in offspring (Gissler et al. 1997). Birth registries are also used as a surveillance tool to evaluate the effects of early life exposures on birth defects. Moreover, the linkage between registers made it possible for researchers to evaluate the effect of different pregnancy complications on the risk of developing later disease such as the link between preeclampsia and developing cardiovascular disease in the future (Wilcox 2007). Birth registries are used to monitor the health of women and their newborns and have provided a valuable infrastructure for evidence base medicine and clinical practice (Olsen 2011). For example, evidence based medicine considerably changed the obstetric practice of breech delivery in Sweden (Alexandersson et al. 2005).

Central Population Register, Cause of Death Register and Medical Birth Register (MBR) cover all live births and stillbirths in Nordic countries, but more detailed information is collected in MBR (Gissler 2010). Along with thalidomide catastrophe, the first national MBR was set up in 1967 in Norway with the purpose of epidemiological surveillance of birth defect (Irgens 2000). Finland established the MBR in 1987 latest than the other Nordic countries. MBR has been used alone or combined with other national birth registries and data from interviews or questionnaires (Gissler et al. 1997). In Finland, perinatal statistics are published every second year by the National Institute for Health and Welfare (THL) which is responsible for birth registers (Gissler 2010).

3.3.2 Strengths and limitations of register-based research

The number of register-based studies have substantially grown. Register-based data have made it easier to develop epidemiological research, especially in the field of rare complications. Detection of rare complications requires large cohort of a hundred thousand to provide enough statistical power. A large number of participants in registries increase statistical power and uncovers the hidden patterns of correlations in rare complications (Olsen 2011). According to Rothman and associates, (2008) large datasets increase the precision of estimation and reduce random error.
Along all advantages of having a large sample size in observational studies, large sample sizes may provide significant results to clinically unimportant associations. Therefore, in analyzing register-based data with a large sample size not only, the statistical significance is important, but also the strength of the association needs to be taken into account (Thygesen & Ersbøll 2014). Additionally, thanks to the unique system of identification numbers, a number of studies has been designed to link data sources to enhance epidemiological and clinical research. These linked datasets sometimes are known as “big data”, but the complexity of big data requires technical and human resources to operationalize data in research practice (Meyer et al. 2014).

One of the objectives of epidemiological studies is to find valid and precise associations between exposures and outcomes. Comprehensive data enable the researcher to understand the underlying mechanisms of different complications and provide opportunities for prevention and treatment. In today's practice, use of register-based data in the Nordic countries and some other countries has made research easier, less time consuming and cost-effective (Irgens 2001). Register-based research represents associations in the real world and the value of register-based data increases over the time periods, because more time and people will be added to the data. For example, in the birth registry as more and more birth accumulated, gave researcher the possibility of evaluating different risk factors on pregnancy outcomes (Wilcox 2007).

Comprehensive register-based data provide an opportunity to consider all confounding factors and give insights into real causal associations. However, this optimal situation is not always the case, because it is not possible to adjust for confounding factors that they are not already exist in the data (Olsen 2011). In register-based study, variable collection is the responsibility of the administrators and the researcher has no controls over the content of variables. Since register-based data are not originally gathered for the research in selected hypothesis, collection of the data may be less precise than the real situation. Additionally, the information of some confounding variables is available in a limited period of time so that incomplete adjustments for potential confounding factors may distort the direction of the associations and affect the quality of the study (Weiss 2011). For example, in Finland, MBR contains information on a limited number of maternal characteristics and birth outcomes and lack of information about maternal weights before 2003 delayed development of appropriate evaluation of maternal weight on pregnancy outcomes (Gissler et al. 1997, Lamminpää 2015). Thus, selection of included variables needs more careful attention. In this regard, the MBR content has been changed three times to improve the quality of
the data and some variables such as maternal background information and outcomes were added into the MBR in 2004 (Räisänen 2011).

Another limitation of register-based data is missing data. Underlying reason for missing data is usually hard to find, but depending on the extent, missing data increases the risk of bias. In handling missing data, having a specific strategy to eliminate the impact of missing values can enhance the interpretation of the result (Gliklich et al. 2014). Moreover, in register-based study, exposure or outcome may be misclassified and this misclassification will happen with the same probability for all study individuals. Consequently, non-differential misclassification of dichotomous variables tends to change the direction of association toward the null and if the exposure is not dichotomous, results may be away from the null (Rothman 2002). From another point of view, since the register-based data have been retrospectively obtained, the information about the exposure is less influenced by later diagnosis of the outcome of interest. Thus, there is less potential for recall bias. For example, register-based studies on the use of medicine in pregnancy, oral contraceptives, is less likely to introduce recall bias (Nørgaard et al. 2009).

Before using the register-based data, reliability and validity of register-based data should be assessed. Validity in the sense that all recorded variables are in the line with the reality. However, in register-based data, sometimes there are variations in the quality of some variables which restrict the usage of variables in statistics and research (Gissler & Haukka 2004). In MBR, the validity of data depends on reporting and they are considered to be valid, if variables have been correctly reported (Räisänen 2011). Additionally, the validity of the registers can be determined by its completeness related to the coverage of all individuals in the registers (Thygesen & Ersbøll 2014). Poor quality of registries may contribute to the suspension of registry such as suspension of the Finnish Register on the Mentally Retarded (Gissler & Haukka 2004).

In public health research, the potential harms of interventions usually stem from physical adverse effects of the intervention, while in register based research, the potential harms of research emanate from overstepping the individuals' privacy. Data in register-based research is anonymous, but the identification of people is not impossible in combination data. Providing high quality data protection ensures confidentiality and minimizes discrimination, stigmatization and social problems in individuals. However, having informed consent from thousands of individuals is not applicable to register-based research and it is time consuming, expensive and sometimes
impossible. Therefore, public benefits of the register-based research should compensate the potential harms to individuals’ autonomy (Eloranta et al. 2015). The combination of all birth registers can provide a good source of collaborative projects especially in rare outcomes. However, there are some variations in the content of registers. Uniform documentation of national registers, such as standardizing the definition of stillbirths or developing cause of infant death, will improve the quality of register-based studies at the international level (Gissler et al. 2010, EURO-PERISTAT 2013). Mutual collaboration between centers and register controllers, coupled with constant use of register-based research as a source of evidence based medicine and decision making will improve the quality of the data (Gissler 2008).
4 AIMS OF THE STUDY

The aim of this registered-based cohort study was to assess the association of AMA with placenta previa, after adjusting for possible maternal and obstetric confounding factors. The second aim of the study was to evaluate the effect of AMA on placenta previa outcomes, including blood transfusion, placental abruption, preterm birth, NICU admission, low birth weight and low Apgar score at 5 minutes, using data of three Finnish health registries from 2004 to 2008, including information of 283,324 women and their newborns. Therefore, the objectives were:

1. To evaluate the association of maternal age ≥35 years old with placenta previa.
2. To compare maternal and neonatal outcomes in AMA women with placenta previa to younger women with placenta previa.
5 METHODS

5.1 Study population
The study was a register-based cohort study, using the data of three Finnish health registries with the information of 283 324 women and their newborns, from 2004 to 2008. The data contained the information about MBR, The Hospital Discharge Register (HDR) and The Register of Congenital Malformations. The information of The Register of Congenital Malformation was used as an exclusion criterion to exclude pregnancies with major congenital anomalies. In addition, women with multiple pregnancies were excluded, because they impose higher risks on pregnancy outcomes. Cross-linkages of registers were done by the use of personal identity codes to increase the completeness of the data.

5.1.1 Medical Birth Register (MBR)
Finland started the Medical Birth Registry in 1987. The MBR covers more than 99.9 % of births in Finland and contains detailed information about previous pregnancies and deliveries, maternal care, diagnosis and interventions as well as newborn health status, diagnosis and interventions up to 7 days. The purpose of MBR is to collect data to improve maternal and neonatal care services in Finland (THL 2015a).

5.1.2 Hospital Discharge Register (HDR)
The HDR was established in 1969. HDR contains information such as hospitalization period, procedure, and diagnosis, on all aspects of inpatient care in public and private hospitals as well as outpatient visits in public hospitals. Diagnoses are coded by using the International Classification of Diseases (ICD) codes (THL 2015b).

5.1.3 Register of Congenital Malformation (RCM)
The Register of Congenital Malformations was established in 1963 and separately liked to MBR. The RCM includes the data on congenital, chromosomal and structural anomalies detected in stillborn and live born infants from all Finnish healthcare settings. The RCM also includes information of abortions due to fetal defects. The register has the follow up period of 6-12 months (THL 2015c).
5.2 Variables and definitions

Variables in the MBR data are usually recorded by nurses or midwives during obstetric visits in pregnancy. In this study, gestational age was estimated by ultrasonography during first and second trimesters or calculated according to last menstrual period. Antenatal visits were categorized as less than 10 visits, 10 to 15 visits and more than 16 visits, since the number of 10 to 15 visits is recommended by Finnish national maternity guidelines. Smoking was self-reported variable and categorized in three categories including non-smokers, smoking only during the first trimester and smoking throughout pregnancy. There was no information regarding the number of cigarettes smoked per day.

5.2.1 Independent variables

Based on the most common definition of AMA, maternal age was categorized into two age groups less than 35 years and 35 years or older, with a reasonable size of the population in both categories. Women less than 35 years were selected as the reference group and this age group contained the median age of women in this population.

For the second aim of this study AMA and placenta previa were considered together as exposure variables. In order to provide better visual evaluation, maternal age was categorized as 20-24 years, 25-29 years, 30-34 years, 35-39 years, 40-44 years and 45-50 years, to assess the unadjusted risk of maternal age on placenta previa outcomes. In addition to AMA, placenta previa was considered as an independent variable. Placenta previa was a dichotomous variable without any further explanation about the type of placenta previa, defined as low-lying placenta covering internal os of cervix. In ICD-10 coding, placenta previa is represented by the O44 diagnosis code. In our population, placenta previa was diagnosed by ultrasound in the second and third trimester and the time of accruing placenta previa was considered as occurring at diagnosis time.

5.2.2 Dependent variables

In assessing the effect of maternal age on placenta previa outcomes, we sets two sets of outcomes, maternal and neonatal outcomes. The main maternal and neonatal outcomes were blood transfusion, placental abruption, preterm birth, NICU admission, low birth weight and low Apgar score at 5 minutes. Placental abruption was diagnosed by clinical examinations and in some
women by ultrasonography. Variable blood transfusion was coded as (yes) for women who received any transfusion of blood products. Infants less than 2500 g were classified as low birth weight. Preterm birth was recorded for births less than 37 weeks of gestation. Apgar scores between 0-6 were recorded as low Apgar scores at 5 minutes. Apgar score is defined by a scoring method and used by birth attendant; a score less than 7 is usually considered a low Apgar score (Apgar 1953). NICU admission was considered when infants were intubated. The second aim of this thesis poses if the risk of adverse maternal and neonatal outcomes of placenta previa increase more in AMA women than younger women.

5.2.3 Confounding variables
The effect of maternal age on placenta previa can be easily distorted by the effect of confounding factors. This distorted effect of confounding factors can overestimate or underestimate the effect of maternal age on placenta previa. In this thesis, in order to deal with the effect of confounding variables, variables were interred in the regression modelling. For the association of AMA and placenta previa parity, smoking, prior Caesarean section, use of ART such as IVF and embryo transfer, Intra-Uterine Insemination (IUI), amniocentesis, were considered as potential confounding variables. In evaluating the effect of age on adverse placenta previa outcomes, parity, smoking, previous Caesarean section as well as obstetric interventions such as use of ART were considered as potential confounding factors.
In this study, preterm birth was not considered as a confounding variable for the association of placenta previa and adverse neonatal outcomes, because preterm birth was in the pathway of the association. Although preterm birth is associated with both placenta previa and adverse neonatal outcomes, preterm birth is a consequence of placenta previa. Therefore, the effect of placenta previa and maternal age on low birth weight, low Apgar score at 5 minutes and NICU admission, considered without adjustment for the gestational duration.

5.3 Design of the study
A registered-based cohort study was performed to assess two research questions. For the first aim of the study, maternal age 35 years or older was considered as exposure and maternal age less than 35 as a reference group. The outcome of interest was placenta previa which is a rare pregnancy
outcome. Thus, a register-based data of three birth registers provided better power to find the association.

For the second aim of the study, in order to assess the unadjusted risk, figures were plotted to evaluate the proportion of adverse pregnancy outcomes with advancing age in women with and without placenta previa. Therefore, figures gave the unadjusted risk of adverse pregnancy outcomes in women with and without placenta previa. In this regard, if the distance of two curves got larger at an advanced age, the hypothesis was correct.

In order to analyze the adjusted risk of adverse pregnancy outcomes in AMA women, placenta previa at AMA women was considered as the main exposure to be studied. We formed four comparison groups, younger women with no previa, younger women with previa, AMA women without placenta previa and AMA with placenta previa, to evaluate what placenta previa and age bring up at the same time.

5.4 Statistical analysis
Statistical analysis was conducted using SPSS version 22. Demographic and clinical characteristics of the study population were compared between women less than 35 years and 35 years or older by using Chi-Square test. The association between advanced maternal age and placenta previa was modelled using a backwards, stepwise logistic regression to calculate adjusted odds ratios and 95% confidence intervals by considering placenta previa as a dichotomous variable. Confounding factors were selected based on literature review or significant associations in bivariate analysis and variables without statistically significant results in bivariate models were checked in logistic regression to ensure the same results. Multivariable logistic regression modelling was used to investigate the association of placenta previa and maternal age with adverse maternal and neonatal outcomes by considering the effect of confounding variables. Results were reported in adjusted odds ratios with 95% CI and P value, with a P value < 0.05 considered significant. The goodness of the final logistic model was examined using the Hosmer–Lemeshow goodness of fit test.

5.5 Ethical considerations
The Ethical approval for this study was gained on 17.05.2016 (THL/151/5.05.00/2016) from THL, which is required by the national data protection legislation.
6 RESULTS

6.1 Characteristics of the studied population

A total of 283,324 women, of which 714 (0.3%) were complicated by placenta previa. 81.2% of women were less than 35 years of age and 18.8% of women were 35 years or older. The median age at delivery was 29, range from 14 to 52 years.

In our population, younger women were more likely single and smokers and older women were more likely multipara. AMA women had higher numbers of antenatal visits, amniocentesis and use of ART like embryo transfer were more common in AMA women. Older women had a higher proportion of pathological glucose tolerance test and were hospitalized more due to bleeding and high blood pressure. Vaginal delivery was performed more in women less than 35 years who were also more likely to have forceps delivery. However, a greater proportion of AMA women had planned and unplanned Caesarean section. There were no statistically significant differences in the proportion of women with anaemia between younger and older group. The demographic characteristics of women are summarized in Table 1.
Table 1. Demographic and clinical characteristics for women giving birth in Finland from 2004-2008, stratified by maternal age.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;35y</th>
<th>≥35y</th>
<th>P value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=230003)</td>
<td>(n=53321)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Single (unmarried, widowed or divorced)</td>
<td>96448(41.9%)(^2)</td>
<td>17682(33.2%)</td>
<td></td>
</tr>
<tr>
<td>Married or in a registered partnership</td>
<td>133357(58.0%)</td>
<td>35591(66.7%)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Primipara</td>
<td>107523(46.8%)</td>
<td>12087(22.7%)</td>
<td></td>
</tr>
<tr>
<td>Multipara</td>
<td>122082(53.2%)</td>
<td>41141(77.3%)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Non-smoking</td>
<td>187420(81.5%)</td>
<td>46561(87.3%)</td>
<td></td>
</tr>
<tr>
<td>Quitted smoking after first trimester</td>
<td>9468(4.1%)</td>
<td>1077(2.00%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>26995(11.7%)</td>
<td>4141(7.8%)</td>
<td></td>
</tr>
<tr>
<td>Embryo transfer</td>
<td>3550(1.5%)</td>
<td>2161(4.1%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Amniocentesis before 25 weeks of gestation</td>
<td>2534(1.1%)</td>
<td>5024(9.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathological glucose tolerance test</td>
<td>18744(8.10%)</td>
<td>7438(14.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Due to high blood pressure</td>
<td>6612(2.9%)</td>
<td>2114(4.0%)</td>
<td></td>
</tr>
<tr>
<td>Due to a threat of prematurity</td>
<td>6795(3.0%)</td>
<td>1427(2.7%)</td>
<td></td>
</tr>
<tr>
<td>Due to bleeding</td>
<td>2452(1.1%)</td>
<td>716(1.3%)</td>
<td></td>
</tr>
<tr>
<td>Due to other reasons</td>
<td>25255(11.0%)</td>
<td>6842(12.8%)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>175680(76.4%)</td>
<td>37643(70.6%)</td>
<td></td>
</tr>
<tr>
<td>Forceps delivery and suction cup</td>
<td>17864(7.8%)</td>
<td>3513(6.6%)</td>
<td></td>
</tr>
<tr>
<td>Planned Caesarean section</td>
<td>14353(6.2%)</td>
<td>5936(11.1%)</td>
<td></td>
</tr>
<tr>
<td>Unplanned Caesarean section</td>
<td>21772(9.5%)</td>
<td>6152(11.5%)</td>
<td></td>
</tr>
<tr>
<td>Number of antenatal visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of antenatal visits more than 15</td>
<td>123659(56.3%)</td>
<td>29402(58.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\) Chi-Square, \(^2\) Values are number and percentage.
6.2 Effect of AMA on placenta previa

Table 2 depicts the association between AMA and other risk factors with placenta previa. The results of regression model showed that AMA was significantly associated with placenta previa AOR 1.54 (1.30-1.83), with a 54% increased risk of placenta previa. Moreover, amniocentesis, IVF, embryo transfer and previous Caesarean section were identified as independent risk factors for placenta previa.

Table 2. The association between advanced maternal age and placenta previa and other risk factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>AOR$^2$ and 95% CI</th>
<th>P-value$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age ≥35y</td>
<td>1.54 (1.30–1.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVF$^4$</td>
<td>7.93 (2.91–21.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Embryo Transfer</td>
<td>5.61 (4.41–7.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other ART$^5$</td>
<td>3.15 (1.16–8.53)</td>
<td>0.023</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>1.68 (1.21–2.33)</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous Caesarean section</td>
<td>1.57 (1.26–1.97)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^1$ Variables included in the model one were maternal age, parity, smoking, previous Caesarean section, IVF, IUI, embryo transfer, other ART and amniocentesis. $^2$ Adjusted Odd Ratio, $^3$ Final model of backwards, stepwise logistic regression. $^4$ In Vitro Fertilization. $^5$ Assisted Reproductive Technology.

6.3 Unadjusted effect of maternal age on placenta previa outcomes

Figure 1 and 2 depict unadjusted risks between maternal age and adverse maternal and neonatal outcomes in women with and without placenta previa. Lower curves illustrate the age-specific risks of maternal and neonatal outcomes in women without placenta previa, while upper curves show age-specific risks of adverse maternal and neonatal outcomes in pregnancies complicated by placenta previa.
Figure 1. Relationship between maternal age and maternal outcomes, by placenta previa (upper curves denote women with placenta previa and lower curves women without placenta previa), from 2004 to 2008 in Finland. (A) Blood transfusion, (B) placental abruption, with 95% CI error bars. Graphs are plotted on the scale of 0-100%.

As Figure 1 depicts, in pregnancies complicated by placenta previa, risks of blood transfusion and placental abruption increased in younger women and decreased in intermediate aged mothers. The effect of AMA compound with placenta previa, leading to increasing risks of blood transfusion and placental abruption in women with placenta previa. The more women delayed the pregnancy, the more they had maternal risks.

As Figure 2 illustrates, risks of neonatal outcomes gradually increased with advancing age in the background population. However, the proportion of adverse neonatal outcomes in pregnancies complicated by placenta previa was not consistent across maternal age groups. It was observed that women aged 40-44 years had the highest risks of preterm birth, NICU admission and low birth weight.
Figure 2. Relationship between maternal age and neonatal outcomes, by placenta previa (upper curves denote women with placenta previa and lower curves women without placenta previa), from 2004 to 2008 in Finland. (A) Preterm birth, (B) NICU admission, (C) low birth weight, (D) low Apgar score at 5 minutes, with 95% CI error bars. Graphs are plotted on the scale of 0-100%.
6.4 Adjusted effect of maternal age on placenta previa outcomes

The adjusted odds ratios for adverse maternal and neonatal outcomes, with considering women without placenta previa as a reference group, are given in Table 2,3. Pregnancies complicated by placenta previa had higher risks of blood transfusion, placental abruption, preterm birth, NICU admission, low birth weight and low Apgar score at 5 minutes, than women without placenta previa. However, the odds for blood transfusion and placental abruption were slightly greater in AMA women with placenta previa than younger women with placenta previa. Furthermore, the magnitude of the associations, for adverse neonatal outcomes, was stronger in women under age 35 with placenta previa, compared with older women counterparts (Table 2, 3).

Table 2. Pregnancy outcomes in women under age 35 with and without placenta previa.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Without placenta previa</th>
<th>With placenta previa</th>
<th>AOR( 95% CI)²</th>
<th>P-value³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>229506(99.8%)¹</td>
<td>496(0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>3710 (1.6%)</td>
<td>67 (13.5%)</td>
<td>6.86 (5.26-8.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>493(0.2%)</td>
<td>12(2.4%)</td>
<td>10.95(6.11-19.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>12532(5.5%)</td>
<td>208(42.0%)</td>
<td>11.76 (9.78-14.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NICU admission</td>
<td>25609(11.2%)</td>
<td>195(39.3%)</td>
<td>4.93 (4.10-5.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>9741(4.3%)</td>
<td>111(22.4%)</td>
<td>5.95(4.77-7.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low Apgar score at 5</td>
<td>4507(2.0%)</td>
<td>28(5.7%)</td>
<td>3.39 (2.29-5.01)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

¹ Values are number and percentage. ² Adjusted Odds Ratio (AOR) and 95% Confidence Intervals (95%CI). Adjusted for parity, smoking, previous Caesarean section, Assisted Reproductive Technology (ART) and Caesarean section. ³ Statistical analysis was conducted with multivariable logistic regression model.
Table 3. Pregnancy outcomes in women aged 35 or older with and without placenta previa.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>without placenta previa</th>
<th>with placenta previa</th>
<th>AOR (95% CI)²</th>
<th>P-value³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>53103 (99.6%)¹</td>
<td>218 (0.4%)</td>
<td>7.31 (5.04-10.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>167 (0.3%)</td>
<td>8 (3.7%)</td>
<td>11.32 (5.48-23.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>3496 (6.6%)</td>
<td>91 (41.7%)</td>
<td>8.84 (6.69-11.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NICU admission</td>
<td>6844 (12.9%)</td>
<td>89 (40.8%)</td>
<td>4.06 (3.08-5.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>2755 (5.2%)</td>
<td>46 (21.1%)</td>
<td>4.06 (2.89-5.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low Apgar score at 5 minutes</td>
<td>1137 (2.1%)</td>
<td>13 (6.0%)</td>
<td>2.78 (1.56-4.96)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

¹Values are number and percentage. ²Adjusted Odds Ratio (AOR) and 95% Confidence Intervals (95%CI). Adjusted for parity, smoking, previous Caesarean section, ART and Caesarean section. ³Multivariable logistic regression.
7 DISCUSSIONS

7.1 Interpretation of the results

In Finland, the proportion of maternal age 35 years or older was 18.8 %, during 2004-2008. Reviewed articles on women age ≥35 years reported different values for the proportion of AMA, ranging from 10.1% in China, to 19% in England and Wales and to 24% in Australia (Crane & Morris 2006, Biro et al. 2012, Xiaoli & Weiyuan 2014).

The results of clinical and demographic characteristic of women were consistent with previous studies and showed that AMA women were more likely to have medical conditions, including high blood pressure and abnormal glucose tolerance which reflects age-related changes in AMA women (Paulson et al. 2002). We found that AMA women had a higher proportion of planned and unplanned Caesarean section. As reported in studies, planned Caesarian section without any indications placed this age group of women in an unnecessary increased risk of adverse pregnancy outcomes. However, induction of labour in women age 35 years or older had no significant adverse effects on maternal and neonatal outcomes (Janoudi et al. 2015, Lavecchia et al. 2016, Walker et al. 2016). Women less than 35 years old in our study were more single and smokers which indicate younger women had more social problems than medical conditions.

Among the total number of women during 2004 to 2008, placenta previa complicated 0.3% of deliveries, which is in the lower range of the reported rates of 0.3–0.5% (Iyasu et al. 1993). We found that AMA was an independent risk factor for placenta previa and several cofactors confounded the association of AMA with placenta previa. In our population, parity and smoking did not confound the association, while in some studies parity and smoking were recognized as strong risk factors for placenta previa (Ananth et al. 2001, Walfisch & Sheiner 2016). In the logistic regression model use of ART was the main risk factor for placenta previa which is consistent with previous studies (Coroleu et al. 2002, Johnston et al. 2015). However, different techniques of ART contributed differently to the risk of placenta previa, IVF and embryo transfer were the most contributing risk factors in the final model. Our finding reinforced that the risk of placenta previa increases with advancing maternal age (Biro et al 2012, Ludford et al. 2012, Liu & Zhang 2014).

From the epidemiological aspects, studies reported higher risk of placenta previa in women aged older than 40 years than women aged 35-39, which means that there is a biological gradient for the association of AMA and placenta previa (Jolly et al. 2000, Cleary-Goldman et al. 2005). One of the explained biological mechanism for increasing the risk of placenta previa in AMA women
is decreasing in the uterine blood flow in older women so that larger place for placenta is needed to provide enough blood flow to the fetus (Ananth et al. 1996).

AMA and placenta previa were accounted as independent risk factors for bleeding. Some studies reported that pregnancies complicated by placenta previa were associated with massive intrapartum, antepartum and postpartum bleeding and the risk was noticeable among women with complete placenta previa (Sekiguchi et al. 2013, Bao et al. 2016). Other studies have identified AMA and Very Advanced Maternal Age (maternal age ≥ 45 years) were independently associated with increased need of blood transfusion (Phadungkiatwattana et al. 2014, Haslinger e al. 2016). The result of these studies did not account for the possible effect of maternal age on the association of placenta previa with blood transfusion. In the current study as illustrated in Figure 1A, apart from high proportion of blood transfusion in early 20s, the proportion of blood transfusion had a gradual increase in AMA women, reaching more than 20% risks of blood transfusion in women aged 40-44 years with placenta previa. After controlling for the effect of confounding variables, including previous Caesarean section, the result supports the concept that AMA women with placenta previa had a higher AOR of blood transfusion than younger women with placenta Previa. This can be partly explained by one in vitro study in which AMA was associated with a decrease in spontaneous uterine contraction (Smith et al. 2008).

Previous reports regarding the risk of placental abruption in AMA women were different. One study reported that the risk of having placental abruption was higher in younger women, while the majority of the analyses found that there is a strong association between AMA and placental abruption (Sheiner et al. 2003, Liu & Zhang 2014). In the current study, the proportion of placental abruption was highest among women aged 20-24 and 40-44 years with placenta previa and this disparity across age groups was not exist in women without placenta previa. However, after adjusting for confounding factors including smoking, the odds ratio of having placental abruption was stronger in AMA women with placenta previa than younger women with placenta previa. The association of maternal age and preterm birth have been accessed frequently and results indicated that the effect of maternal age on preterm delivery had the familiar U-shaped pattern with high risks of preterm delivery in adolescents and older women (Ferré et al. 2016). Although studies indicated higher risks of preterm birth in AMA women and pregnancies complicated by placenta previa (Zlatnik et al. 2007), in our study, the risk of preterm birth in women with placenta previa was not additive with advancing maternal age. In the study of Lawlor and associates (2011),
the lowest rate of preterm birth across age groups was reported among women aged 24-30 years. Whereas, in the current study in women with placenta previa, mothers aged 20-24 years had the lowest proportion of preterm birth.

Since preterm birth is more common in pregnancies complicated by placenta previa, it may affect the risk of other adverse outcomes. In other words, preterm delivery is an intermediate or surrogate outcome on the causal path from placenta previa to low birth weight, low Apgar score at 5 minutes and to NICU admission. Thus, in this study in order to prevent overadjustment which increases the net bias, preterm birth was considered as an intermediate outcome on the causal path from placenta previa to neonatal outcomes (Schisterman et al. 2009).

In previous studies, the risks of LBW had a U-shaped pattern across age groups, with high risk of LBW in younger and older mothers, at two ends of maternal age. In the unadjusted model, the proportion of LBW infants in pregnancies complicated by placenta previa across age groups had the same pattern with the highest proportion of LBW among mothers age of 40-44 years (Figure 2 C). In this study, the presence of placenta previa in pregnancy increased the risk of an infant being admitted to NICU, which is consistent with the result of a recent systematic review (Vahanian et al. 2015). In previous studies, the risks of NICU admission were not affected by AMA, but one study reported that AMA women with preeclampsia had higher risks of NICU admission than women less than 35 years with preeclampsia (Lamminpää et al. 2012). In our study the odds of NICU admission in women less than 35 with placenta previa were higher than AMA women with placenta previa, which means age-related outcomes may be differently affected in various complications during pregnancy.

In neonatal outcomes after controlling for the effect of gestational age on low birth weight and low Apgar score, the causal associations disappeared. Therefore, in pregnancies complicated by placenta previa, low birth weight and low Apgar score are mediated by the real effect of gestational age and there were no other significant causal associations. One explanatory reason for the higher rate of preterm birth and other related complications in younger women with placenta previa is that AMA women have lower oxytocin receptor than younger women so that the contractility of the uterus decreases in older mother and the uterus is less susceptible to premature contracting process of preterm birth (Lisonkova et al. 2011).
7.2 Strengths and weaknesses

The main strength of this study is the number of participants. A large number of participants in this study provided the possibility of considering important confounding factors and studying sufficiently rare outcomes. Placenta previa is a rare pregnancy complication consequently a large sample size is needed to detect small differences in risks between two groups of maternal age. Additionally, the comprehensiveness of this data made it possible to consider the effect of different techniques of ART on placenta previa. From another point of view, since placenta previa is a rare pregnancy complication, there is a possibility of being under-reported based on antenatal routines. However, the data were drawn from well-established registries and there was only one missing case for the variable placenta previa. According to Gissler and Haukka (2004), the register-based data in Finland have adequate coverage and validity. On the other hand, the data were not originally collected for this study hypothesis and information on the severity and grade of placenta previa were not available. The information on low Apgar score at 5 minutes was missing in 15.2% of participants. Therefore, the result of this variable needs to be interpreted with caution. There is no information about the level of education for considering socioeconomic characteristic of the participants as a confounding factor. As previously discussed, AMA women are more educated and the level of education may have positive effects on the outcomes.

7.3 Generalizability of the results

The results of this study are generalizable to other population in which healthcare services are freely and similarly available to all women. Finland has ethnically homogenous population and the results can be generalized to populations with similar structure. Furthermore, the effect of risk factors on placenta previa may have substantial variations between countries, because of differences in baseline characteristics of the studied populations. For example, disparity in the rate of Caesarean section, from 16% in Finland to 38% in Italy, can affect the magnitude of the risks among populations (EURO-PERISTAT 2013). Thus, the generalizability of the results requires careful thought, because risk factors of placenta previa may contribute differently to the risk of placenta previa across countries.
7.4 Implications for practice

The results of this study showed the effect of age on the risk of placenta previa and determined how AMA can affect the observed risks of placenta previa outcomes. The results emphasized more on the effect of AMA on maternal morbidity and adverse outcomes. Thus, growing trends toward postponing pregnancy in many countries could be an emerging public health concern and need to be taken more seriously. It is necessary to inform women about possible adverse effects of postponing motherhood, while respecting women's reproductive autonomy (Lemoine & Ravitsky 2015).

AMA women usually want to have optimal birth outcomes, because they have postponed childbearing to the older age or they underwent ART. However, the occurrence of comorbidities in AMA women may negatively affect pregnancy outcomes. The results of this study indicated that AMA women had a higher possibility of using ART or having preexisting medical conditions. Additionally, AMA independently affected the risk of other complications such as placenta previa and may worsen the risk of blood transfusion and placental abruption in pregnancies complicated by placenta previa. These comorbidities may further influence the risk of adverse pregnancy outcomes and pose major challenges for healthcare professionals. Therefore, the finding of this study will provide additional guidance for clinicians to identify high-risk groups in order to improve prenatal, antenatal and neonatal care of older age women.

Based on the literature review, one of the main causes of haemorrhage in pregnancy is placenta previa and pregnancies complicated by placenta previa had a higher risk of placenta accreta. Based on the results of current thesis, higher risks of placental abruption and blood transfusion were expected in pregnancies complicated by placenta previa especially in AMA women. Hence, detailed examination of placental morphology by early ultrasound screening is necessary to rule out placenta accreta (Moretti et al. 2014). Moreover, sufficient preparation for blood transfusion is needed to prevent further maternal and neonatal adverse outcomes in pregnancies complicated by placenta previa.

7.5 Implications for research

This study presented the effect of AMA on placenta previa as well as the effect of maternal age on adverse pregnancy outcomes of placenta previa in Finnish women from 2004 to 2008. The results showed that AMA is a risk factor for many pregnancy complications and it is recommended to
include maternal age in risk factor analyses of pregnancy outcomes in research. Although, AMA is a risk factor for many adverse pregnancy outcomes, it is not clear whether increased risks of adverse pregnancy outcomes are due to age-related changes in the uterus or due to other risk factors. Assessing the combined effect of AMA with other risk factors such as socioeconomic status on pregnancy outcomes is needed to provide sufficient evidence for maternal practices.

Based on the results of the study, the magnitude of ART risks was greater than other risk factors for placenta previa and different techniques of ART contributed differently to the risk of placenta previa. For example, the adverse effect of IVF was stronger than embryo transfer and the strength of associations were stronger than other studies. Therefore, further research may be needed to evaluate the effect of different techniques of ART on placenta previa and placenta previa outcomes in Finnish population.

Placenta previa is a costly complication. Higher risks of adverse maternal outcomes in women with placenta previa, higher risks of emergency Caesarean section, longer stay in hospital due to Caesarean section as well as higher risks of preterm birth and NICU admission impose more costs on families and healthcare systems. From another point of view, AMA increases the length of maternal and fetal hospitalization and consequently increases both direct and indirect costs. Direct costs from prolonged maternal hospitalization and indirect cost related prematurity of infants, maternal complications and cost related to amniocentesis (Haslinger et al. 2016). Therefore, both placenta previa and pregnancies in older women contribute substantially to adverse pregnancy outcomes and place an economic burden on families and healthcare systems. Therefore, further studies are needed to examine the costs related to placenta previa and other risk factors such as AMA and to explore how costs can be eliminated.
8 CONCLUSIONS

The results of this large population based study showed that AMA was an independent risk factor for placenta previa, increasing the risk of placenta previa by 54%. The results of this thesis supported the association of placenta previa with IVF, embryo transfer, amniocentesis and previous Caesarean section.

We hypothesized that placenta previa coupled with age-related changes in the uterus may worsen pregnancy outcomes. This study addressed an important gap in evidence, to our knowledge, the effect of maternal age on placenta previa outcomes has not previously assessed. In this regard, the effect of AMA on placenta previa was presented in the adjusted and unadjusted models. In general, women with placenta previa were at increased risks of adverse pregnancy outcomes in comparison to women without placenta previa. The results of the unadjusted model suggested that the risk of adverse pregnancy outcomes in women with placenta previa was not uniform across maternal age groups. The results of adjusted models confirmed that the combination of placenta previa and AMA were associated with slightly increased risks of blood transfusion and placental abruption. In contrast, younger women with placenta previa had greater risks of preterm birth, NICU admission, low birth weight and low Apgar score than AMA women with placenta previa.

Overall, the results of this thesis suggested that postponing of childbearing in Finnish mothers increased the risk of placenta previa and the combination of placenta previa with AMA may have a marginal effect on the risks of blood transfusion and placental abruption.
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