Tampere University

ILARI KUITUNEN

Total Hip Replacement and Reproductional Health

An analysis based on combined national register data

Tampere University Dissertations 163

Tampere University Dissertations 163

ILARI KUITUNEN

Total Hip Replacement and Reproductional Health

An analysis based on combined national register data

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty od Medicine and Health Technologies
Tampere University,
for public discussion in the auditorium Väinö Linna - sali
of the Linna building, Kalevantie 5, Tampere,
on 13th December 2019, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health Technologies
COXA Hospital for Joint Replacement
National Institute of Health and Welfare
Finland

Responsible supervisor	Docent Antti Eskelinen Tampere University Finland	
Supervisors	Docent Miia Artama Tampere University Finland	Docent Eerik Skyttä Tampere University Finland
Pre-examiners	Docent Riitta Luoto Tampere University Finland	Docent Veli-Matti Ulander University of Helsinki Finland
Opponent	Docent Rami Madanat University of Helsinki Finland	
Custos	Assistant professor Ville Mattila Tampere University Finland	

The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-1328-9 (print)
ISBN 978-952-03-1329-6 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-1329-6

PunaMusta Oy – Yliopistopaino
Tampere 2019

To my family

ABSTRACT

Total hip replacement (THR) is a highly effective operation for reducing pain and improving quality of life. An increasing number of patients are fertile-aged at the time of primary THR operation. There have only been a few previous studies that have analyzed reproductive health after THR. These studies have mainly focused on delivery method after THR, survival of the implant after delivery, and whether maternal THR increases the risk for congenital anomalies in the offspring. None of these studies have reported decreased implant survivorship or THR complicating delivery. There are two case reports in which congenital anomalies have been found in the offspring of women with metal-on-metal THR. These cases were considered to be hereditary. All previous studies have either been case reports or small local case series.

The overall aim of our retrospective cohort study was to analyze reproductive health after THR in a nationwide setting. In study I, we analyzed the birth rate after THR in male and female patients. The risk for pregnancy ending in IA after primary THR was addressed in study II. Study III aimed to analyze delivery and neonatal health after maternal THR. Congenital malformations in the offspring of THR patients were analyzed in study IV. The impact of delivery on THR survival was analyzed in study V.

The participants in this study were gathered from six national registries. The registers included in our study were as follows: the Finnish Arthroplasty Register, the Medical Birth Register, the Register of Induced Abortions, the Register of Congenital Malformations, the Register or Medical Reimbursements, and the Population Information System. Information on THRs was obtained from 1980 to 2007 and information on pregnancies was gathered from 1987 to 2007. A total of 2 429 fertile-aged (15 to 45 years) women at the time of THR were included and 3 434 fertile-aged (15 to 50 years) men. For every patient, three matched referents (7 276 women and 10 299 men) without implants were identified and these formed the reference group. In statistical analyses, logistic regression models, Kaplan-Meier survival analysis, and Cox proportional hazard models were used.

The probability for live birth was decreased after THR compared with the reference group in study I. The adjusted hazard ratio for the first children after THR for women was 0.56 (95% confidence intervals (CI) 0.46 – 0.68) and for men 0.80 (95% CI 0.69 – 0.92). In study II, the women had no increase in risk for pregnancy ending in IA after THR compared with reference group, adjusted odds ratio 1.50 (95% CI 0.99-2.28), although the women were more likely to end their pregnancy due to maternal health issues (14.3% vs. 2.7% of the IAs). Cesarean section (CS) was a significantly more common delivery method in the THR patient group in study III (CS rate 52.9% vs. 19.3%). A higher proportion of the deliveries were preterm (adjusted OR 3.58 (95% CI 2.03 – 6.30)) and neonates were more likely to be born small-for-gestational-age (OR 2.83 (95% CI (1.35 – 5.93)) (study III). The risk for congenital anomalies was not increased in the offspring of THR patients (OR 3.93 (95% CI 0.76 – 20.2, p=0.13). Delivery does not decrease THR survivorship (adjusted hazard ratio 1.12 (95% CI 0.77 – 1.62)).

Our results suggest that delivery does not adversely affect THR survival. THR patients (both men and women) have lower birth rates after THR compared with the reference group. However, the risk for induced abortions is not increased among women with THR. THR clearly affects the choice of delivery method, and CS proportion is significantly higher after THR. It seems that adverse pregnancy outcomes are more common in the offspring of THR patients. The risk for congenital anomalies was not, however, increased. Future studies should also focus on the effects of metal-on-metal implants on reproduction.

TIIVISTELMÄ

Lonkan tekonivelleikkaus on tehokas ja kustannusvaikuttava toimenpide, ja hyvien tuloksien myötä, näitä leikkauksia tehdään yhä enemmän myös nuorille, fertiili-ikäisille potilaille. Aiempia tutkimuksia tekonivelleikattujen fertiili-ikäisten naisten ja miesten lisääntymisterveydestä on vain muutamia. Nämä aiemmat tutkimukset ovat keskittyneet lähinnä analysoimaan synnytystapaa leikkauksen jälkeen, tekonivelen pysyvyyttä synnytyksen jälkeen ja riskiä vastasyntyneen epämuodostumiin äidin tekonivelleikkauksen jälkeen. Näissä tutkimuksissa ei ole raportoitu tekonivelen vaikeuttavan synnytystä, eikä synnytyksen heikentävän tekonivelen pysyvyyttä. Epämuodostumia on raportoitu kahdessa potilastapauksessa, mutta molemmissa niitä pidettiin tekoniveleen liittymättömänä. Kaikki aiemmat tutkimukset ovat kuitenkin olleet lähinnä potilastapauksia tai pieniä paikallisia potilassarjoja.

Tämän kohorttitutkimuksen tavoitteena oli selvittää kansallisella tasolla koko maanlaajuisia rekisteritietoja hyödyntäen retrospektiivisesti lonkan tekonivelleikkauksen vaikutusta kokonaisvaltaisesti lisääntymisterveyteen. I osatyössä selvitimme tekonivelen vaikutusta fertiliteettiin. II osatyössä tutkimme lisääkö lonkan tekonivel riskiä raskaudenkeskeytyksille. III osatyössä analysoimme synnytyksiä ja vastasyntyneen syntymäterveyttä ennen ja jälkeen tekonivelleikkausta. IV osatyössä tutkimme lisääkö äidin tekonivel riskiä synnynnäisille epämuodostumille. V osatyössä selvitimme synnytyksen vaikutusta lonkan tekonivelen pysyvyyteen.

Aineistomme koostui kuudesta eri rekisteristä. Tekonivel-, syntymä-, raskaudenkeskeytys- ja epämuodostuma rekisterit ovat Terveyden ja Hyvinvoinnin laitoksen (THL) ylläpitämiä. Lisäksi hyödynsimme Kelan erityiskorvattavuus tietoja pitkäaikaissairauksista ja väestörekisteriä verrokkiryhmän poimintaan. Tekonivelleikkaukset kerättiin vuosilta 1980-2007. Tiedot raskauksista ja vastasyntyneistä ovat vuosilta 1987-2007. Tutkimusryhmän muodostivat 2 429 naista (leikkauksen aikana iältään 15-45 vuotta) ja 3 434 miestä (iältään 15-50 vuotta), joille oli leikattu lonkan tekonivel. Verrokkiryhmään kuului 7 276 naista ja 10 299 miestä, joilla ei ollut tekoniveltä ja jotka olivat iältään ja asuinpaikaltaan kaltaistettuja tutkimusryhmään. Tilastollisina analyyseinä käytettiin jakauman mukaisten

tunnuslukujen ja testausten (t-testi, Mann-Whitney U, Khiin neliö) lisäksi logistisia regressiomalleja, Kaplan-Meierin elinaika-analyysiä ja Coxin riskimallia.

I osatyössä havaitsimme, että lonkan tekonivelpotilaiden leikkauksen jälkeinen lapsensaanti oli alentunutta verrattuna verrokkeihin. Naisten vakioitu riskitiehyssuhde saada lapsi leikkauksen jälkeen oli 0.56 (95% luottamusväli 0.46 – 0.68) ja miesten vakioitu riskitieheyssuhde0.80 (95% lv 0.69 – 0.92). II osatyössä osoitimme, että naisilla oli raja-arvoisesti lisääntynyt riski raskaudenkeskeytyksiin tekonivelleikkauksen jälkeen (vakioitu vedonlyöntisuhde 1.50 (95% lv 0.99-2.28)), vaikka tutkimusryhmässä suurempi osauus raskaudenkeskeytyksistä olikin äidin terveyden vuoksi (14.3% vs. 2.7%). III osatyössä tutkimusryhmässä oli selvästi suurempi osuus keisarinleikkauksia (52.9% vs. 19.3%). Lisäksi synnytykset olivat useammin ennenaikaisia (vakioitu vedonlyöntisuhde 3.58 (95% lv 2.03 – 6.30)) ja vastasyntyneet pienempipainoisia viikkoihin nähden (vakioitu vedonlyöntisuhde 2.83 (95% lv (1.35 – 5.93)). IV työssä riski synnynnäisille epämuodostumille ei ollut kohonnut tutkimusryhmässä (vedonlyöntisuhde 3.93 (95% lv 0.76 – 20.2, p=0.13). V osatyössä näytimme, että synnytys ei heikennä lonkan tekonivelen kestävyyttä (vakioitu riskitiheyssuhde uusintaleikkaukselle 1.12 (95% lv 0.77 – 1.62)).

Näiden tuloksien perusteella voimme todeta, että synnytys ei vaikuta lonkan tekonivelen pysyvyyteen. Lisäksi, fertiliteetti on verrokkiväestöä pienempää tekonivelleikkauksen jälkeen, sekä miehillä, että naisilla. Alentunutta syntyvyyttä ei selitä kuitenkaan lisääntynyt riski raskaudenkeskeytyksille, vaan pienempi lukumäärä raskauksia tekonivelpotilailla leikkauksen jälkeen. Tekonivelleikkaus vaikuttaa selvästi naisen synnytystapaan. Vastasyntyneiden syntymäterveys vaikuttaisi olevan heikompi tutkimusryhmässä, mutta riski epämuodostumille ei ole kohonnut. Riskiä epämuodostumiin ja hidastuneeseen sikiön kasvuun voisi tarkentaa jatkotutkimuksissa erityisesti metalli-metalli lonkkatekonivelen saaneilla potilailla.

CONTENTS

ABBREVIATIONS

ARMD	Adverse Reaction to Metal Debris
BMI	Body Mass Index
CI	Confidence Interval
CS	Cesarean Section
CoC	Ceramic-on-ceramic
CoM	Ceramic-on-metal
CoP	Ceramic-on-polyethylene
DDH	Developmental Dysplasia of the Hip
DM	Diabetes Mellitus
FAR	Finnish Arthroplasty Register
GDPR	General Data Protection Regulation
HR	Hazard Ratio
IA	Induced Abortion
ICD-10	International Classification of Diseases version 10
KELA	The Social Insurance Institution of Finland
LBW	Low-birth-weight
LGA	Large for Gestational Age
MBR	Medical Birth Register
MoM	Metal-on-metal
MoP	Metal-on-conventional polyethylene
MoXLP	Metal-on-highly cross-linked polyethylene
OA	Osteoarthritis
OR	Odds Ratio
PD	Proportion Difference
PIS	Population Information System
PROM	Patient Reported Outcome Measure
PYRS	Person years
SD	Standard Deviation
SES	Socioeconomic Status
SGA	Small for Gestational Age

RA	Rheumatoid Arthritis
RIA	Register for Induced Abortions
RMR	Register for Medical Reimbursements
RR	Risk Ratio
THL	National Institute of Health and Welfare
THR	Total Hip Replacement
TOPFA	Termination of pregnancy due to fetal anomaly
VLBW	Very-low-birth-weight

ORIGINAL PUBLICATIONS

Publication I Artama Miia, Skyttä Eerik, Huhtala Heini, Leino Mikko, **Kuitunen Ilari**, Eskelinen Antti. Lower birth rate in patients with total hip replacement. Acta Orthop. 2016 Oct;87(5):492-6. doi: 10.1080/17453674.2016.1193396. Epub 2016 Jun 1

Publication II **Kuitunen Ilari**, Skyttä Eerik, Eskelinen Antti, Huhtala Heini, Artama Miia. Induced Abortions Among Women Having Undergone Total Hip Replacement: A Nationwide Register Study in Finland. Scand J Scand J Surg. 2019 Sep;108(3):258-264. doi: 10.1177/1457496918812229. Epub 2018 Nov 16.

Publication III **Kuitunen Ilari**, Artama Miia, Eskelinen Antti, Skyttä Eerik, Huhtala Heini, Uotila Jukka. Pregnancy outcome in patients after total hip replacement: a population-based study. Eur J Obstet Gynecol Reprod Biol. 2019 Jul;238:143-147. doi: 10.1016/j.ejogrb.2019.05.020. Epub 2019 May 20

Publication IV **Kuitunen Ilari**, Eskelinen Antti, Skyttä Eerik, Huhtala Heini, Artama Miia. Congenital anomalies in the offspring of women with total hip replacement – a nationwide register study in Finland (Accepted for publication)

Publication V **Kuitunen Ilari**, Skyttä Eerik, Artama Miia, Huhtala Heini, Eskelinen Antti. The effect of pregnancy and delivery on total hip replacement survival: a nationwide register study in Finland. Acta Orthop. 2019 Oct;90(5):433-438. doi: 10.1080/17453674.2019.1628561. Epub 2019 Jun 21.

1 INTRODUCTION

Total hip replacement (THR) is a highly effective operation to reduce pain and to improve the quality of life of patients (Harris & Sledge, 1990; Rissanen, Aro, Slatis, Sintonen, & Paavolainen, 1995). Indeed, THR has been described as the operation of the 20th century (Learmonth, Young, & Rorabeck, 2007). Because of the success of THR, an increasing proportion of patients are fertile-aged (under 50 years) at the time of primary THR (Kurtz et al., 2009). In young patients, the most common indications for THR are rheumatoid arthritis (RA), developmental hip diseases, and avascular necrosis of the femoral head (Adelani, Keeney, Palisch, Fowler, & Clohisy, 2013; Hannouche et al., 2016).

Although the number of fertile-aged patients has increased, little is known about the effects of THR on reproduction. To date, no previous studies have analyzed birth rate after THR. THR is known to improve the sexual quality of life of hip patients, although it remains lower compared with persons without THR. THR does, however, affect sexual intercourse by reducing the number of possible positions (Klit, Jacobsen, Schmiegelow, Sonne-Holm, & Troelsen, 2015; Stern et al., 1991). Moreover, chronic diseases, such as RA and DM, have been shown to reduce the fertility rate (Sjöberg, Pitkäniemi, Haapala, Kaaja, & Tuomilehto, 2013; Wallenius et al., 2011). In addition, chronic diseases also increase the risk for spontaneous abortions. The risk for induced abortions, however, seems to be similar to that found in healthy women (Blais, Kettani, & Forget, 2013; Kjaer, Hagen, Sandø, & Eshøj, 1992; Vinet, É, Kuriya, Pineau, Clarke, & Bernatsky, 2013). It could be possible therefore that THR reduces fertility rates.

Previous studies of THR and fertility have focused mainly on delivery methods after THR. There have been a few case reports and small case series that suggest that normal delivery after THR is possible (Lally, Mandl, Huang, & Goodman, 2015; Reckling, 1976; Sierra, Trousdale, & Cabanela, 2005; Yazici et al., 2003; Yoon, H. J., Yoo, Yoon, Koo, & Kim, 2012). A few studies have also reported that women elect to be delivered by caesarean section due to the fear of vaginal delivery damaging the THR implant (Meldrum, Feinberg, Capello, & Detterline, 2003; Ostensen, 1993;

Stea, Bordini, De Clerico, Traina, & Toni, 2007). None of these studies, however, reported any delivery-related or neonatal complications.

There have also been previous case reports on the possible teratogenic effect of the metal-ions released from metal-on-metal (MoM) THR. Metal-ions have been detected entering the fetal blood circulation. Moreover, the concentration of umbilical cord metal-ions has been reported to be elevated compared with the reference fetuses of women without THR (deSouza, Wallace, Costa, & Krikler, 2012; Fritzsche, Borisch, & Schaefer, 2012; Novak et al., 2014; Ziaee, Daniel, Datta, Blunt, & McMinn, 2007). Two case reports have reported congenital anomalies in the offspring of women with MoM THR (Brodner et al., 2004; Oppermann, Borisch, & Schaefer, 2015). Other case reports have reported normal health neonates without anomalies, even though the neonate metal-ion concentrations have been elevated and have remained elevated for weeks (Fritzsche et al., 2012).

Although pregnancy and delivery place a great deal of stress on the pelvis (Smith, M., Marcus, & Wurtz, 2008), it seems that neither pregnancy nor delivery decrease THR survivorship (McDowell & Lachiewicz, 2001; Meldrum et al., 2003; Sierra et al., 2005; Stea et al., 2007; Yazici et al., 2003). A single case report has described revision performed after pregnancy due to aseptic loosening (Boot, Heyligers, & Heins, 2003). Interestingly, delivery does not seem to affect or decrease patient reported outcome measures (PROMs) in THR patients (Lally et al., 2015; McDowell & Lachiewicz, 2001; Meldrum et al., 2003; Stea et al., 2007). However, increased groin pain has been reported during pregnancy among women with THR (Sierra et al., 2005).

2 REVIEW OF THE LITERATURE

2.1 Total Hip Replacement

The concept behind this common operation is simple, although the operation itself cannot be described as simple. During the operation, the head and proximal neck of the femoral bone are removed surgically, and a canal is created in the medullary space of the femoral bone. The femoral part of the prosthesis is then inserted into the femoral medullary canal. The acetabulum in the pelvis is enlarged using a reamer instrument and a cup is inserted into the created space. The bearing surfaces of the implants may vary, but they are designed to have long endurance as well as low friction. (Siopack & Jergesen, 1995) The goal of the operation is to decrease pain, restore functionality, and improve quality of life, and the operation has been shown to achieve this goal with excellent results (Harris & Sledge, 1990; Rissanen et al., 1995).

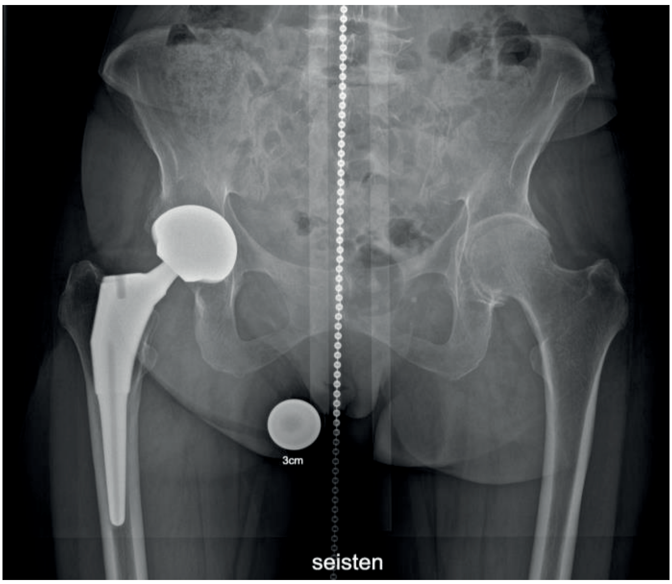


Figure 1. Total hip replacement in the right hip and normal femur and acetabulum in the left hip in an anterior X-ray image of a female patient.

2.1.1 History of THR, briefly

Total hip replacement (THR) has been described as the operation of the 20th century (Learmonth et al., 2007). The first attempts to operate lower limb traumas without amputation, however, were reportedly done as early as the 19th century. Hip osteotomies were then performed, where the whole joint was removed and manipulated to cause pseudarthrosis. The first operative attempts to treat osteoarthritis (OA) were done in late 1890 when JB Murphy performed a hip cheilectomy, where bone osteophytes were removed from the femoral caput and acetabulum. In the early 1900s, the first interpositional hip arthroplasties were performed. A variety of methods and materials (pig bladder, gold) were tried before M. Smith-Petersen provided the first mold arthroplasties. (Gomez & Morcuende, 2005) At first, the mold was surfaced with glass, but in 1938 the vitallium cup was invented. This signaled the start of a new era of arthroplasties (Hernigou, 2014; Learmonth et al., 2007).

In the same year, P. Wiles performed the first total hip replacement where stainless steel was used, and the fixation of the implant was done using screws and bolts (Gomez & Morcuende, 2005; Learmonth et al., 2007; Mellon, Liddle, & Pandit, 2013). Later, Wiles and others experimented with many types of materials ranging from stainless steel to rubber, glass, and ivory (Mellon et al., 2013). K. McKee introduced the first proper metal-on-metal (MoM) bearing THR in the 1950s (Triclot, 2011). However, the first case report on a metallic hip prosthesis had been published already in 1943, where half of the femur was removed due to a tumor and replaced with an identical metallic prosthesis (Moore and Bohlman, 1943).

In the late 1950s and early 1960s, Sir John Charnley revolutionized hip prosthesis operations with his low friction arthroplasty (Charnley, John, 1961). At the time, it had by far the best survival rates of all implants. Charnley was the first to use polymethyl methacrylate cement to fix the implants into the bone (Knight, Aujla, & Biswas, 2011). Today, the principle of modern THR is still the same as Charnley's low friction arthroplasty (Knight et al., 2011; Learmonth et al., 2007; Mellon et al., 2013). Charnley´s implant gained popularity over McKee's MoM THR due to its better implant survival rates (Mellon et al., 2013). Charnley made a significant effort to understand prosthesis surgery and prosthesis failure, and he is also credited with the discovery of the theatre air microbes that cause prosthesis infections (Charnley, John, 1964).

From the 1980s onwards, alternative bearings, such as metal-on-metal (MoM) or ceramic-on-ceramic (CoC), have been introduced with the aim of improving performance (Triclot, 2011). The CoC implant was designed with harder bearing surfaces to decrease wear, but it is less commonly used due to high costs and squeaking (Knight et al., 2011). MoM implants are discussed in more detail later. Less invasive techniques as well as cementless fixations have also gained in popularity in recent years (Courpied & Caton, 2011). Currently, a metal head combined with a highly cross-linked polyethylene is the most common bearing couple used in contemporary THRs (AOANJRR, 2019; NJR, 2018; SHAR, 2019; THL, 2018c).

2.1.2 Indications / diagnosis for THR

2.1.2.1 Indications in all ages

In the beginning, THR was mostly used to treat the pain and dysfunction caused by rheumatoid arthritis (RA) and primary osteoarthritis (OA) in elderly active people. Due to the advances in the medical treatment of RA, RA is now a relatively rare indication for THR in older patients. (Mellon et al., 2013) In 2017, the most common indications for primary THR in Finland were primary OA (86.2%), fracture of the femoral neck (4.4%), avascular necrosis of the femoral head (3.0%), RA (1.3%), and developmental dysplasia of the hip (DDH) (1.3%) (THL, 2018c). Between 1995 and 2011, the most common indications were primary OA (82.4%), RA (4.6%), and hip fracture (3.7%). The proportion of hip fractures was much lower in Finland (4.4%) compared with the proportions of other Nordic countries (11.7 - 13.9%), whereas the proportion of primary OA diagnosis in Finland (86.2%) was higher (73.0 - 78.7%). (Mäkelä et al., 2014b)

2.1.2.2 Indications of young patients

According to a recent review, for young patients (aged under 30 years at the time of THR), the most common indications for THR after 1988 were avascular necrosis of the femoral head (34.8%), juvenile RA (25.4%), DDH (14.6 %), and Perthes´ disease (5.4 %). Before 1988, the most common diagnoses were juvenile RA (49.5 %), DDH (10.6%), following posttraumatic OA (8.2%), and avascular necrosis (7.6%) (Adelani et al., 2013). In a retrospective study, the most common indications for patients aged under 20 years old were avascular necrosis of the femoral head (56.2%), slipped capital femoral epiphysis (11.4 %), and DDH (10.5 %) (Hannouche et al., 2016). Another study in the same age group (<20 years) had the same three indications in the same order as the most common diagnoses for THR: avascular necrosis, slipped upper femoral epiphysis, and DDH. (Patel, Luff, Whittingham-Jones, Gooding, & Hashemi-Nejad, 2012) A recent large Scandinavian register study combined all the Nordic arthroplasty registers and analyzed primary THRs performed on patients aged under 21 years at the time of the operation. In their study, the following diagnoses were the most common: pediatric hip diseases (including DDH and Perthes) (33%), systemic inflammatory disease (juvenile RA + other arthritis) (23%), avascular necrosis of the femoral head (12%), hip fracture sequelae (7%), osteoarthritis (4%), and other diagnoses (21%) (Halvorsen et al. 2019). (Figure 2)

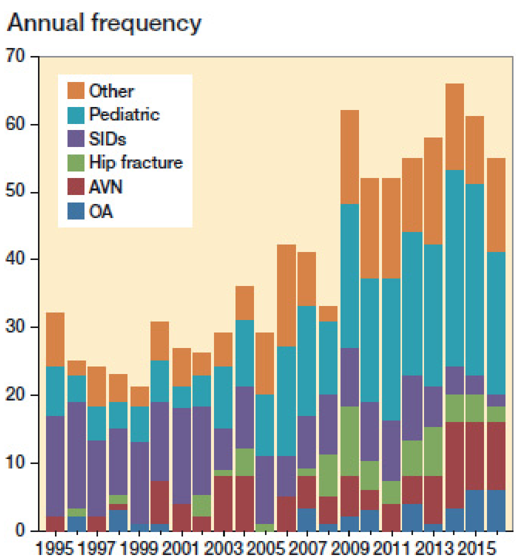


Figure 2. Indications from 1995 to 2016 of primary THR in patients aged under <21 years old. Other: tumors, sequelae after infection, pharmaceutically induced femoral necrosis. Pediatric: developmental dysplasia of the hip (DDH), Perthes, slipped capital femoral epiphysis (SCFE). SIDs: systemic inflammatory diseases including rheumatoid arthritis, ankylosing spondylitis, and other inflammatory diseases. AVN: avascular necrosis. OA: osteoarthritis.

Borrowed from the original source: Halvorsen V, Fenstad AM, Engesæter LB, Nordsletten L, Overgaard S, Pedersen AB, Kärrholm J, Mohaddes M, Eskelinen A, Mäkelä KT & Röhrl SM (2019) Outcome of 881 total hip arthroplasties in 747 patients 21 years or younger: data from the Nordic Arthroplasty Register Association (NARA) 1995–2016, Acta Orthopaedica, 90:4, 331-337, DOI: 10.1080/17453674.2019.1615263

2.1.3 Incidence and prevalence of THR

In Finland, a total of 10 102 primary THRs and 1 725 revision THRs were performed in 2017. Of these, 562 women and 665 men were aged under 55 years at the time of primary THR. During our study period (from 1987 to 2007), the total numbers have increased. In 1987, 281 women and 143 men aged under 55 had primary THR. In 2007, the numbers were 442 women (52.3% increase) and 543 men (279% increase), showcasing the increase in incidence of THR, especially among men. (THL, 2018c)

During our study period, the total incidences for primary THR in all age groups increased significantly from 153 per 100 000 person years in 1987 to 300 per 100 000 person years in 2007. The current overall incidence for primary THR was 398 per 100 000 person years in 2017. In the youngest age group (<55 years), the current incidences were 120 per 100 000 person years for men and 113 per 100 000 person years for women. In 1987, the incidences were 28 for men and 52 for women. The increase was seen already in 2007 when it was 91 for men and 82 for women. (THL, 2018c)

The incidences for younger patients (30-39 years old) have not, however, increased as much as the incidences for middle-aged (40-49 years old) patients in Finland. For middle-aged patients, the increase from 1980 to 2007 was 6 times higher than in the younger group. The incidence for primary THR was 5 per 100 000 person years in 2007 for the youngest age group. (Skytta, Leskinen, Eskelinen, Huhtala, & Remes, 2011) In the UK in 1996, the incidences for patients under 40 years old were 2.1 per 100 000 person years for women and 1.3 per 100 000 person years for men (Dixon, Shaw, Ebrahim, & Dieppe, 2004).

In the US, the overall prevalence of the THR among females aged under 50 has risen from 0.03% in the 1980s to 0.10% in the 2010s and among males from 0.05% to 0.12% (Maradit Kremers et al., 2015). The prevalence in Sweden for patients aged under 40 years was 12 THRs per 100 000 person years in 1999 and 19 THRs per 100 000 person years in 2012 (Cnudde et al., 2018). Therefore, THR can be said to be relatively rare among fertile-aged patients, since the majority of the patients who undergo this otherwise common operation are elderly. In the United States, it has been estimated that the primary THR rate in the youngest age group (<45 years old) could possibly grow 3-fold by 2030 compared with 2006 rates. This would mean 46 900 primary THRs every year for fertile-aged males and females. Without this expected growth, the THR rate would be a constant 15 600 THR per year for this age-group. (Kurtz et al., 2009)

2.1.4 Contemporary THR

2.1.4.1 Different bearing couples, fixations and techniques

The most common bearing couple used in modern THR is metal-on-highly cross-linked polyethylene (MoXLP). Other possible bearing couples are metal-on-conventional polyethylene (MoP), metal-on-metal (MoM), ceramic-on-ceramic (CoC), ceramic-on-polyethylene (CoP), and ceramic-on-metal (CoM) (López-López et al., 2017). For patients of all ages who underwent THR in the UK between 2003 and 2017, the most popular bearing surfaces in primary THR were MoXLP (58.8%), followed by CoP (17.5%), CoC (14.7%), MoM (7.2%), and other (including CoM) (1.6%). The most common implant type in the UK was the all cemented MoXLP, which comprised 29.6% of all the primary THRs. (NJR, 2018) The different types of implant bearing/fixation combinations used are shown in Table 1.

Of the implants operated in Finland in 2017 for patients under 55 years, 69.9% were uncemented, 1.5% cemented, 20.5% reverse hybrids, and 5.0% hybrids by fixation type (THL, 2018c). In the NJR report of patients of all ages who underwent THR between 2003 and 2017, the proportions of fixations were uncemented (38.9%), cemented (34.2%), hybrid (20.2%), reverse hybrid (2.6%), and resurfacings (4.0%). (NJR, 2018).

The current MoP bearing couple is based on Charnley's low friction arthroplasty. In this design, the bearing of the acetabular cup is polyethylene and the bearing of the femoral stem is metal. (Charnley, John, 1961; López-López et al., 2017). The polyethylene can be either highly cross-linked or not highly cross-linked. However, the highly cross-linked polyethylene performs better than the not highly cross-linked. Hence, highly cross-linked polyethylene is currently more commonly used. (AOANJRR, 2019; Marques et al., 2016; NJR, 2018; SHAR, 2019; THL, 2018c)

Ceramic surfaces were introduced with high hopes of excellent durability and a low rate of wear (Hannouche, Zaoui, Zadegan, Sedel, & Nizard, 2011). Although the survival rates of CoC and CoP THRs have been at least similar compared with MoP THRs (D'Antonio, Capello, & Naughton, 2012; D'Antonio, Capello, & Naughton, 2014), survival rates are still much lower than MoP THRs (AOANJRR, 2019; NJR, 2018; SHAR, 2019; THL, 2018c). In addition, there are problems, such as squeaking, impingement, and ceramic ruptures, associated with the CoC implant, (Migaud et al., 2016; Salo, P. P. et al., 2017).

Overall, the different implants have been shown to have quite similar survival rates with the exception of a few significantly worse bearing/fixation combinations. In a large meta-analysis (López-López et al., 2017) and in large register-based studies (Smith, A. J., Dieppe, Howard, & Blom, 2012; Smith, A. J., Dieppe, Vernon, Porter, & Blom, 2012a), cemented large-head MoM THRs and MoM resurfacings were found to have an especially higher risk for revision. MoM bearings are discussed in more detail in chapter 2.1.4.3.

The surgical techniques for THR have evolved. The use of the direct-lateral approach with patients in supine position has decreased. Instead, the antero-lateral approach in lateral decubitus (Hardinge approach) and the posterior approach have gained popularity (Cnudde et al., 2018). In Finland, 87.2% of the primary and 89.1% of revision THRs were performed using the posterior approach in 2018. The other technique commonly used in Finland was the Hardinge approach (12.2%). (THL, 2018c)

Table 1. Possible combinations of total hip replacement (THR) bearings and implant fixations used in the 21st century. Modified from the original sources (Marques et al., 2016; NJR, 2018) MoXLP= Metal-on-highly cross-linked polyethylene, MoP= Metal-on-polyethylene, MoM= Metal-on-metal, CoC= Ceramic-on-ceramic, CoP= Ceramic-on-polyethylene, CoM= Ceramic-on-metal.

Bearing materials	Fixation
MoXLP	Cemented
	Uncemented
	Hybrid
	Reverse hybrid
MoP	Cemented
	Uncemented
	Hybrid
	Reverse hybrid
MoM	Cemented
	Uncemented
	Hybrid
	Resurfacing
CoC	Uncemented
	Hybrid
CoP	Cemented
	Uncemented
	Hybrid
	Reverse hybrid
CoM	Uncemented

2.1.4.2 Bearing wear and its consequences

All implants have been shown to have bearing wear. These particles cause all kinds of harm and reactions to periprosthetic tissues and also have other possible systemic effects. Already in the 1970s and 1980s, the wear of polyethylene components were reported in a follow-up study of Charnley THRs by Charnley himself (Charnley, J. & Halley, 1975; Salvati et al., 1981). The effect of these wear particles has been discussed for the last three decades. In the early 1990s, many reports and studies were published on the local effects of polyethylene wear. Polyethylene wear was shown to cause bone loss and osteolysis, which could have caused implant component loosening. (Bankston, Faris, Keating, & Ritter, 1993; Schmalzried, Jasty, & Harris, 1992; Schmalzried, Jasty, Rosenberg, & Harris, 1994) In 1994, Harris described these finding as particle diseases, where the wear particles from the THR (either polyethylene or metal) cause local problems (Harris, 1994).

The etiology for the osteolysis are the extremely fine polyethylene wear particles released from the MoP or CoP THR (Jasty et al., 1994). In in vitro analysis, the submicron-sized polyethylene particles were similar to those found in in vivo analysis of the patients, and the particles were shown to cause osteolysis (McKellop et al., 1995). These ultrafine particles cause local inflammation in soft tissues and bones that, in turn, leads to osteolysis (Goodman, 2007; Massin & Achour, 2017).

Pseudotumors have been mostly associated with MoM bearings. However, since the tumors were also found among patients with low blood concentrations of Cr and Co, it was considered whether there might be other factors that cause pseudotumor other than the released metal-ions. (Hjorth et al., 2018) A recent study focused on adverse reaction to metal debris (ARMD) in patients with bilateral MoM THRs and showed that although the significantly differing amounts of wear was seen between the sides, majority of the histological findings were similar bilaterally and pseudotumors were found symmetrical in most cases (although the wear rate differed between sides). Therefore, they suggest that the host response to metal debris is individual and that the presence of ARMD might be due to a delayed hypersensitivity reaction to metal ions (Lehtovirta et al., 2019). A few case reports have been published in recent years where pseudotumors were found among patients with MoP, CoP, and CoC THRs (Bisseling, Tan, Lu, Campbell, & van Susante, Job L C, 2013; Campbell, Rajaee, Brien, & Paiement, 2017; Carli, Reuven, Zukor, & Antoniou, 2011; Scully & Teeny, 2013; Serrano et al., 2018). One recent study with a rather small study sample suggested that pseudotumors could also be common in MoP THRs (Hjorth et al., 2018). However, this finding has not been confirmed by others. The wear of MoM implants is discussed in the next chapter 2.1.4.3.

The aim of the implant manufacturers and scientists has been to reduce wear and the release of these harmful particles and to improve implant durability. Many alternative tribology designs have been presented. (Chang, 2014) For example, highly cross-linked polyethylene reduces the wear rate significantly compared with standard polyethylene (Beksaç, Salas, González Della Valle, & Salvati, 2009; Devane et al., 2017). Highly cross-linked polyethylene had lower rates of wear and no signs of osteolysis in a ten-year follow-up study, where it was compared with MoM, standard MoP, and CoC bearings (Atrey et al., 2017).

2.1.4.3 Metal-on-Metal bearing

The first generation MoM THR was introduced in the 1950s by McKee and Watson-Farrar (McKee & Watson-Farrar, 1966). The implant was used for a while until the Charnley low-friction MoP THR gained popularity due to better results and because the McKee implant struggled with implant loosening (Triclot, 2011). The interest in alternative bearings again evolved in the 1980s (Singh et al., 2013), mostly due to the polyethylene wear of MoP implants and osteolysis (Gallo, Raska, Mrázek, & Petrek, 2008; Noordin & Masri, 2012). The second generation MoM was introduced by Weber in 1988 (Weber, 1992), and early results were reported to be excellent (Weber, 1996). In the 1990s, the next generation of hip resurfacing arthroplasties with large diameter heads were introduced. These were believed to have lower wear, lower risk for dislocation and fractures, and easier revisions (McMinn, 2003). The promising early results of these resurfacing arthroplasties led to the introduction of the large diameter MoM THR. The large-diameter MoM was initially used as a revision implant for dislocated THR (Lombardi, Skeels, Berend, Adams, & Franchi, 2011), but gained popularity due to good first experiences, and by 2010, 35% of the primary THRs in the US were MoM THRs (Singh et al., 2013). In 2012, it was estimated that over one million MoM hip replacements had been implanted globally (AAOS, 2012).

As adverse tissue reactions had already been described shortly after the introduction of MoM implants (Evans, Freeman, Miller, & Vernon-Roberts, 1974), the introduction of large-diameter MoM THRs lasted for less than a decade before the first reports of tissue defects were published (Ollivere, Darrah, Barker, Nolan, & Porteous, 2009; Park et al., 2005a; Willert et al., 2005). Although these reports were published in the mid-2000s, it was not until 2010 that the real debate about the problems with MoM implants began, and the British authorities published a medical device alert due to soft tissue reactions caused by metallic wear from the MoM implants (MHRA, 2010). The ASR implants were recalled by the company before the poor survival results (6-year revision rate for ASR THR was 48.8%) were published by the National Joint Register (Langton, Jameson et al., 2011).

The main problems with MoM THRs were caused by bearing surface metal particle wear. The released metal ions are very harmful, and are generally referred to as adverse reactions to metal debris (ARMD). (Natu, Sidaginamale, Gandhi, Langton, & Nargol, 2012) ARMD include metallosis, pseudotumors, inflammatory responses, and necrosis (Lari Lehtovirta et al., 2018). ARMD are seen in both high- and low-wear implants (Langton, Joyce et al., 2011), but the rate of these reactions is high among patients with MoM THR (Reito, Puolakka, Elo, Pajamäki, & Eskelinen, 2013).

The metallic wear from the MoM THR is composed of mainly cobalt and chromium ion particles. The concentrations of these ions in the blood of patients with MoM THR have been reported to be elevated compared with patients without THR, the first reports of which were published already in 1980 (Daniel, Ziaee, Pradhan, Pynsent, & McMinn, 2007; Dobbs & Minski, 1980; Sauvé et al., 2007). Moreover, the ion levels are also significantly higher when compared with patients with MoP THR or patients without THR (Dahlstrand et al., 2017). However, the metal-ion concentrations decrease after the MoM THR is revised and changed to a non-MoM bearing couple (Lainiala, Reito et al., 2015). The concentration of these ions is also increased in other body fluids, such as synovial fluid, whole blood, serum, plasma, erythrocytes, and urine (Hartmann et al., 2013; Lehtovirta et al., 2017).

The first case reports of patients having symptoms associated with pseudotumors caused by local inflammatory reactions to MoM THRs were reported in the late 2000s (Clayton et al., 2008; Shahrdar, 2011; Watters et al., 2010). The prevalence of these pseudotumors was much higher than expected (Bosker et al., 2012). These pseudoutumors are detected by MRI (Lainiala et al., 2014) and ultrasound (Lainiala, Elo et al., 2015). Pseudotumors may cause pain and discomfort in the groin but also periprosthetic soft tissue destruction and even neurovascular compressions (Hasegawa et al., 2016).

Regarding osteolysis, the same principles are present in MoM THRs than in MoXLP, MoP and CoP, or CoC. Already in 2005, early osteolysis was reported among patients with second-generation MoM THRs. At that time, some authors suggested that it might be associated with hypersensitivity to metal. (Park et al., 2005b) Histological analyses of revised MoM THRs showed metallosis as a reaction to metal debris (Korovessis, Petsinis, Repanti, & Repantis, 2006). Osteolysis was later described as an immunological reaction to metal wear debris (Delaunay, Petit, Learmonth, Oger, & Vendittoli, 2010). Blood Cr and Co levels have been shown to correlate with bearing wear volume and also to the degree of necrosis and macrophage infiltration in periprosthetic tissues, suggesting a dose-response relationship (Lari Lehtovirta et al., 2018)

There has been a debate on whether MoM implants might increase cancer risk due to the possible carcinogenic effect of Cr and Co ions. In 1991, the first Finnish study was published in which patients with McKee MoM implants were found to have different types of cancers than people without THR, but with no overall increase in rates of cancer (Visuri & Koskenvuo, 1991). Following this, a large

Finnish cohort study was published in 1996, where MoM patients had a slightly but not significantly elevated incidence ratio for cancer (Visuri, Pukkala, Paavolainen, Pulkkinen, & Riska, 1996). As the second-generation MoM THRs and resurfacing arthroplasties gained popularity and ARMD became more common, newer large cohort studies were conducted in the UK and Finland. None of these nationwide large cohorts reported an increase in cancer risk among MoM THR patients compared with THR patients with other bearing types or people without THR (Ekman et al., 2018; Hunt, Blom, Matharu, Porter, & Whitehouse, 2018; Mäkelä et al., 2012; Mäkelä et al., 2014a; Smith, A. J., Dieppe, Porter, & Blom, 2012).

2.1.4.4 Metal ions and pregnancy

The metal ions released from MoM THRs are mainly Cr and Co. Other ion levels remain low. In animal studies, elevated Cr ion blood levels have been shown to be toxic to the fetus and to cause malformations (Junaid, Murthy, & Saxena, 1995; Kanojia, Junaid, & Murthy, 1998). Co has been shown to have genotoxic and teratogenic effects (De Boeck, Kirsch-Volders, & Lison, 2003; De Boeck et al., 2003; Kasten, Mullenders, & Hartwig, 1997). Moreover, according to two studies, the ions released from MoM THRs to the synovial fluid have the potential to cause chromosomal damage to human cells in laboratory cultures (A P Davies et al., 2005; Daley, Doherty, Fairman, & Case, 2004). In a systematic literature review among industrial workers, exposure to Cr was reported to cause reproductive health problems and pregnancies were more likely to end in miscarriage (Keegan, Learmonth, & Case, 2008)

The first study to investigate neonate outcome after maternal MoM THR and to report serum metal-ion levels was published in 2004 (Brodner et al., 2004). In their case series, three fertile-aged women with 3 pregnancies were followed and blood samples analyzed at delivery. Maternal blood samples had slightly increased Cr and Co concentrations, but the umbilical cord samples had concentrations below their detection limits (DL). However, the samples were analyzed using atomic absorption spectrometry that detects low concentrations worse than the inductively-coupled plasma mass spectrometry used in the other studies (Case, Ellis, Turner, & Fairman, 2001). One of the neonates in this study had major multiform anomalies that were considered hereditary because the mother had had two previous children with congenital anomalies.

Ziaee et al. (2007) contacted 100 fertile-aged patients that had MoM THR operated between 1997 and 2006. Of these women, 10 reported being pregnant and participated in the study. For these 10 patients, they selected 10 referents without metal implants and compared their maternal and umbilical cord blood metal-ion levels between groups. As suspected, the MoM THR group had higher metal-ion levels in the maternal blood and umbilical cord. None of the neonates had any congenital anomalies in this study. (Ziaee et al., 2007) Later, in 2014, Novak et al. published a case series of elevated maternal blood metal-ion levels during pregnancy. In their study, a reference group was also present and comparisons of Cr and Co levels were made during delivery for both maternal and umbilical cord blood in both groups. In this study, the MoM THR group's metal-ion levels were higher than in the reference group without metal implants. No congenital anomalies were detected in this study. (Novak et al., 2014) Both of these studies reported similar transfer rates of metal-ions from maternal blood to umbilical cord blood but concluded that the placenta prevents the major passage of these ions. For example, in the reference group, the transfer rates were over 90% and in the MoM patients the placenta reduced the passage rates to between 10 and 50% (Novak et al., 2014; Ziaee et al., 2007). In their case series, DeSouza et al. (2012) presented three mothers with MoM hip resurfacing arthroplasties without a reference group. Cr and Co ion levels were slightly higher than in the previous three studies, but the transfer rate was similar. No anomalies were detected, and all the neonates were reported to be healthy when released from hospital. (DeSouza et al., 2012)

The highest metal-ion concentrations were reported by Fritzsche et al. (2012) in a case report. The Co concentration was 50 times higher than in any other previous case report of maternal samples, and Cr levels were 10 times higher. In this study, the transfer rates during delivery were similar to previous reports, and also led to higher fetal Co and Cr levels at birth. They also reported the Cr and Co levels of the children at 8 weeks of age. During those 8 weeks, Co levels had already decreased significantly from a high of 75 at the time of delivery to 13 at 8 weeks and Cr levels remained the same as those at birth (2.1 and 2.5). No anomalies were detected in this study. (Fritzsche et al., 2012). Oppermann et al. (2015) present similar high levels of Co and Cr with similar transfer rates in their case report. They detected a neonate born with major congenital anomaly that needed surgical treatment later. This is the only study to present metal-ions concentrations in breast milk. Co levels were high in milk, but Cr levels were below detection limit, which was 1.0ng/ml. At 9 weeks postpartum, the child's Co levels had decreased from 31 at birth to 10, but Cr levels continued to rise from 2.3 to 6.7 during the same period. (Oppermann et al., 2015)

All of these studies present similar transfer rates of metal-ions from the maternal blood to umbilical blood. The placenta prevents major passage of these ions. However, the modulatory rate of the placenta also has limits. The most important previously published literature regarding metal-ion levels in delivery and neonates are summarized in Table 1.

Johnson et al. retrospectively contacted 48 female patients aged under 40 at the time of hip resurfacing MoM-arthroplasty operated between 1996 and 2010. A total of 8 women reported 17 pregnancies with 14 deliveries and 3 miscarriages. In this study, no information on maternal or umbilical cord metal-ion levels was available. Of those 14 neonates, none had any delivery related problems or congenital anomalies, and in later follow-up they were reported to have normal developmental status matching to their ages at the time of the survey (1 to 11 years). (Johnson, Woon, Le Duff, & Amstutz, 2013)

Table 2. Most important previously published literature on metal-ions release from MoM implants and the effect on pregnancy and neonates

Study	Brodner et al. 2004	Ziaee et al. 2007	Fritsche et al. 2012	DeSouza et al. 2012	Novak et al. 2014	Oppermann et al. 2015
Study design	Case series	Case series	Case report	Case series	Case series	Case report
No. of patients	3	10	1	3	3	1
Metal ion concentrations (ng/mL)						
-Maternal	Cr 0.5-1.6 Co -1.0	Cr 1.28 (mean) Co 1.39 (mean)	Cr 20 Co 143	Cr 4.8-7.3 Co 2.2-9.8	Cr 1.02-2.47 Co 0.43-1.25	Cr 25 Co 51
-Umbilical cord	Cr below DL (0.3) Co below DL	Cr 0.38 (mean) Co 0.84 (mean)	Cr 2.1 Co 75	Cr 1.1-1.7 Co 1.0-4.7	Cr 0.16-0.44 Co 0.23-0.67	Cr 2.3 Co 31
-Breast milk	N/A	N/A	N/A	N/A	N/A	Cr below DL (1.0) Co 8.1
-Neonate	N/A	N/A	Cr 2.5 (8 weeks of age) Co 13	N/A	N/A	Cr 6.7 (9 weeks of age) Co 10.0
Transfer rate from maternal blood to umbilical cord						
-Chromium	-	0.29	0.11	0.21-0.23	0.16-0.18	0.09
-Cobalt	-	0.60	0.52	0.46-0.52	0.53-0.54	0.61
Reference group	No	Yes	No	No	Yes	No
Anomalies detected	Yes (1 case had multiple anomalies)	No	No	No	No	Yes
Conclusion	Placenta inhibits the metal ions from entering the fetal circulation.	Placenta prevents majority of these ions entering the fetal circulation	Elevated umbilical blood Cr and Co levels at birth	Elevated umbilical blood Cr and Co levels at birth	Placenta prevents majority of these ions entering the fetal circulation	Child was born with congenital anomaly, but relation to MoM remains unclear

2.1.5 THR implant survival

2.1.5.1 Reasons for failure

In 2018, over 1 500 revision THRs were performed in Finland. The most common indications for revision THR in all age groups were as follows: infection (21.7%), dislocation (19.7%), periprosthetic femoral fracture (12.9%), aseptic loosening of the acetabular cup (11.7%), and adverse reaction to metal debris (ARMD) (11.1%). The proportion of the revisions due to ARMD has decreased from 17.8% in 2014, whereas the proportion of revisions for infections (15.9% in 2014) and dislocation (12.4%) have increased. (THL, 2018c)

According to a systematic review, which included 16 studies between 1965 and 2011 with 115 patients aged under 30 years old at the time of primary THR, the most common indications for revision THR were aseptic loosening (60.9%), wear (12.2%), infection (10.4%), instability (5.2%), and femoral component fracture (3.5%). The review compared results before and after 1988 and the proportion of revisions due to loosening has decreased (70.7% before and 48.0% after). However, revisions due to instability (0% before and 12.0% after) and wear (3.1% before and 24.0% after) have increased (Adelani et al., 2013). Another study that included 92 patients under 30 years of age, compared revision indications for older patients (>60 years) and found that risk for revision was similar for deep infections, aseptic loosening, and periprosthetic fractures. Risk for revision due to MoM implants also increased, mainly due to higher rates of MoM implants among very young patients. (Makarewich, Anderson, Gililland, Pelt, & Peters, 2018) In a Norwegian study, the most common reason for revision THR among extremely young (<20 years old) patients were aseptic loosening and wear (Tsukanaka et al., 2016). In a recent Scandinavian study, the most common revision indications for patients aged under 21 years at the time of THR were aseptic loosening (52%), other (31%), luxation (9.3), deep infection (5.1%), and periprosthetic fracture (2.5%) (Halvorsen et al. 2019).

2.1.5.2 Young age and implant survival

Very young patients at the time of primary THR have worse survival and clinical outcomes than older patients, although the results have improved over the decades (Adelani et al., 2013). Younger patients place higher demands on the THR due to higher activity levels, and therefore the implants have increased rates of aseptic loosening and more bearing wear (Clohisy, Calvert, Tull, McDonald, & Maloney, 2004; Kearns, Jamal, Rorabeck, & Bourne, 2006). A New Zeeland study found that patients aged under 50 have a higher risk for revision THR than dying, whereas the risk is 50-50 for 58 year old patients, and at the age of 62 years the patient is already more likely to die before revision THR. Therefore, younger patients should be warned that revision THR is likely to be needed during their lifetime. (Wainwright, Theis, Garneti, & Melloh, 2011)

For males under 55 years of age, implant survival rates in Finland were 10 years 85.8 %, 15 years 75.1%, and 20 years 62.6%. For women, the survival rates were lower: 10 years 80.7%, 15 years 67.9%, and 20 years 56.0%. (THL, 2018c) An American study examined THR survival rates among patients aged under 35 years operated due to osteonecrosis of the hip. A total of 135 patients were included and implant survival rates were 85.6% at 10 years, 76.7% at 15 years, and 66.3% at 20 years. In stratified analysis, patients aged under 25 years at the time of operation had decreased survival rates compared with those aged over 25 years (Swarup et al., 2017) Patients aged less than 20 years at the time of operation had a 70% implant survival rate at 10 years in a Norwegian register study (Tsukanaka et al., 2016). Another study surveyed implant survival of CoC THRs among patients aged less than 20 years at the time of the THR. They reported a 10-year survival rate of 90.3% (95% CI 82.4 – 98.9). The number of patients included was 83 with 105 THRs, and the patients were operated between 1979 and 2013. (Hannouche et al., 2016) A large register-based study showed that every additional year of age at the time of THR decreased the risk for revision due to aseptic loosening by 1.8% (Münger, Röder, Ackermann-Liebrich, & Busato, 2006).

A study of the combined Nordic arthroplasty registers showed that the overall implant survival rates in patients under 21 years of age have decreased compared with older patients. The survival rates did not differ by the primary THR indication. Cemented and uncemented THRs had similar implant survivorship in this study. The overall implant survival rate was 86% at 10 years. (Halvorsen et al. 2019)

2.1.5.3 Factors affecting implant survival

The diagnosis affects THR implant survival. A large Norwegian register study found that after adjustments the following diagnoses had the worse survival rates compared with primary osteoarthritis: fracture of the femoral neck, congenital dislocation, and a heterogenous group of rare diagnoses. (Furnes, O. et al., 2001) Patients diagnosed with developmental dysplasia of the hip have, for example, had lower implant survival than THRs operated due to any another diagnosis (Tsukanaka et al., 2016). Comorbid diseases also decrease implant survivorship (Jämsen, Peltola, Eskelinen, & Lehto, 2013).

Fixation technique also has an impact on implant survivorship. Uncemented implants seem to have a decreased risk for aseptic loosening in the long-term compared with cemented and hybrid implants, but in the short-term, cemented implants were superior (Pedersen et al., 2014). A Swedish register study suggested that a cemented THR has better survival than an uncemented THR (Hailer, Garellick, & Kärrholm, 2010). In the Finnish arthroplasty register, the 10-year revision rates for cemented implants among patients under 55 years is 18.4% (95% CI 16.8 – 20.1%) and 17.0% (95% CI 16.4-17.7%) for uncemented implants (THL, 2018c).

Bearing couples were discussed in detail earlier in chapter 2.1.4.1. To sum up the literature on bearing couples, MoM implants have inferior mid- and long-term results compared with non-MoM implants, and MoM implants cause adverse local tissue reactions due to released metal-ions. CoC bearing couples have been reported to have excellent results in terms of implant survival, but patients report squeaking and noise from these implants (Salo, P. P. et al., 2017). Metal on polyethene implants are the most commonly used bearings, although the PE tends to wear. (López-López et al., 2017) However, the highly crosslinked PE has provided more promising results in terms of wear than traditional conventional PE, and therefore the MoXLP is the most used combination in contemporary THR (AOANJRR, 2019; Johanson et al., 2017; NJR, 2018; SHAR, 2019; Teeter et al., 2017; THL, 2018c).

Weight and height are not independently associated with poorer implant survivorship results. However, in a European study it was reported that one unit increase in BMI has an odds ratio (OR) of 1.03 (95% CI 1.00-1.05) for implant revision. (Münger et al., 2006) A Norwegian study reported that overweight is associated with a significantly increased risk of revision (RR) of 2.5 (95% CI 1.0–6.3) (Flugsrud, Nordsletten, Espehaug, Havelin, & Meyer, 2007). A German study also showed that a higher BMI decreases implant survivorship (Fuchs & Wieder, 2000).

An American study suggested that rates of revisions or implant removals and common complications after primary THR were strongly associated with BMI (Wagner, Kamath, Fruth, Harmsen, & Berry, 2016). Patients with a high BMI (over 35) have worse PROMs after surgery compared with patients with a normal BMI (Wu et al., 2016).

In Finland, women aged under 55 years have lower mid- and long-term implant survival rates than men. The same is also seen in older age groups in Finland. (THL, 2018c). In a European multinational register study, women had a lower risk for revision due to aseptic loosening of the stem or cup (Münger et al., 2006).

Patients with higher activity levels have a higher risk for implant revision due to aseptic loosening of the stem than those with lower activity levels (Münger et al., 2006). Men have a higher risk for aseptic loosening of the implant, especially if the patient has high levels of physical activity (Flugsrud et al., 2007). Generally, patients with higher activity levels have similar survival rates, at least for the short- and mid-term (Jassim, Douglas, & Haddad, 2014; Lübbeke et al., 2014). Patients are, however, more likely to reduce their sporting activities after joint replacement surgery (Jassim et al., 2014; K Huch et al., 2006; Ritter & Meding, 1987).

2.1.5.4 Influence of pregnancy and delivery on THR survival

Since pregnancy places stress on the pelvis and can cause, for example, transient osteoporosis of the hip and lead to spontaneous hip fracture (Asadipooya, Graves, & Greene, 2017; Beaulieu, Razzano, & Levine, 1976; Bhardwaj & Nagandla, 2014). Also breastfeeding changes bone metabolism and might reduce bone mass and cause transient osteoporosis leading to fractures (Holmberg-Marttila et al., 1999; Kovacs CS. 2014; Miyamato et al., 2019). A study conducted in Thailand suggested that bone density in hip would decrease after 4-6 months lactation (Teerapornpuntakit et al., 2017). Especially if Vitamin D levels are low and BMI in not normal at the beginning of the pregnancy (Yoshikata et al., 2019). Recent studies however have suggested that breastfeeding does not reduce bone density and mass as much as previously suspected (Cooke-Hubley et al., 2017). There has been a concern that pregnancy and delivery could decrease the survivorship of the THR. One concern has also been that during vaginal delivery the flexion of the hip as well as possible rotations during pushing might loosen or dislocate the hip (Sierra et al., 2005). Indeed, women have concerns that delivery and pregnancy might affect the THR negatively (Meldrum et al., 2003; Ostensen, 1993; Sierra et al., 2005).

The first proper study to focus on THR after delivery was a case series by McDowell et al. that presented five pregnant women with seven THRs having six successful pregnancies. The patients were compared to five matching THR patients without pregnancies. They surveyed PROMs, implant survivorship, and radiographic outcomes. No harm caused by delivery to the THR was detected during their eight-year follow-up. This was the only study to also report radiographic outcomes after delivery. (McDowell & Lachiewicz, 2001)

Yazici et al. published the first larger case series in 2003 where they retrospectively contacted fertile-aged women operated between 1981 and 1988. A total of 21 women reported to have been pregnant after THR and had 20 deliveries. None of the 21 women reported any THR related problems. However, no long-term results or survival rates were reported. (Yazici et al., 2003) Similar results were reported by Meldrum et al. in 2003 in their 13 patient case series. They also evaluated PROMs after deliveries and found no decrease in implant survivorship or PROMs compared with THR patients without deliveries. (Meldrum et al., 2003)

In 2003, the first and only case report of delivery possibly harming THR was published. In this case report, the patient became pregnant one year after primary THR. The THR was performed through a posterolateral approach, using a hydroxyapatite coated stem and cup with additional screws and autograft of the femoral head. During the pregnancy, the patient was evaluated by her orthopedic surgeon, and at three months gestation the hip was clinically normal. The orthopedic surgeon recommended vaginal delivery to avoid any possible wound infections. During delivery, extreme flexion and internal rotation should be avoided. For obstetric reasons, CS was performed. In the next control, four months postpartum, the THR had signs of aseptic loosening, which resulted in revision THR six months postpartum due to the loosening. No signs of infections were detected. The association between the pregnancy/delivery and aseptic loosening, however, remained speculative and unlikely. The next pregnancy and delivery did not harm the revised THR. (Boot et al., 2003)

The largest study on THR survival after delivery was published in 2005. Sierra et al. presented a case series of 47 patients with 52 THRs who gave birth after THR. They retrospectively contacted all fertile-aged women who had undergone THR between 1975 and 1995. A Kaplan-Meier survival model was presented for the whole study population instead of a comparison between women who had delivered after THR and those who had not. This was the only study to present the implant survival results in a Cox model. In their study, delivery did not increase the risk for revision. Young age was the only significant factor decreasing implant survivorship in their model of the following variates: preoperative diagnosis, type of implant, and age at the time of THR. Delivery method (CS vs vaginal) did not affect implant survivorship. They also reported that hip and groin pain that continued after pregnancy predicted revision THR compared to those who did not suffer pain after pregnancy. (Sierra et al., 2005)

In 2007, Stea et al. published a case series of 14 patients to present THR results after delivery. The authors retrospectively contacted 143 fertile-aged (at the time of THR) women and used a telephone questionnaire to evaluate pregnancies after THR was performed. In total, 14 patients had 19 pregnancies after primary THR. In this small series, delivery did not harm the survival of the THR and only one of the 14 THRs were revised during follow-up. Unfortunately, the authors did not report the follow-up period, nor did they report the results of the Cox regression model they conducted (Stea et al., 2007).

The most recent study on this topic was published by Lally et al. in 2015. The aim of the study was to report the pain and function of the hip after delivery compared with THR patients without deliveries. The primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores. They compared results between three group: no pregnancies at all, pregnancy before THR, and pregnancy after THR. Only ten women reported pregnancy after THR. Interestingly, these ten women reported better or similar WOMAC scores in pain and function than those in the other groups. Implant survivorship was not discussed in this study. (Lally et al., 2015) The key findings and main results of all of the most important previously published literature are presented in Table 3.

Table 3. The most important previously published studies on THR survivorship after delivery

Author	Study period	Study design	No. of patients	No. of hips	No. of deliveries	Main outcome measure(s)	Main Outcome	Comment
McDowell et al. (2001)	N/A	Case series	5	7	6	Implant survivorship, PROMs, clinical status and radiographic findings	No harm caused to THR due to delivery in any measurement	Only study to present radiographic outcomes
Yazici et al. (2003)	1981-1988	Case series	21	N/A	20	Implant survivorship	No decrease in survival	No long-term results presented
Boot et al. (2003)	N/A	Case report	1	1	2	Implant survivorship	After first pregnancy revision, THR was done due to aseptic loosening	Only study to report problems with THR after delivery
Meldrum et al. (2003)	1981-2000	Case series	13	17	20	Implant survivorship and PROMs	No decrease in survival. PROMs were equal	
Sierra et al. (2005)	1975-1995	Case series	47	52	47	Implant survivorship, pain during pregnancy	No decrease in survival. 60% of the patients reported increased groin pain during pregnancy	Only study to present proper survival rates and Cox model
Stea et al. (2007)	1990-2005	Case series	14	14	14	Implant survivorship and PROMs	No decrease in survival PROMs were at equal	No cox model presented
Lally et al. (2015)	2007-2011	Cohort	10	10	10	PROMs	Delivery does not decrease post-operative pain or function PROMs	No implant survivorship analyzed

2.2 Fertility

2.2.1 Birth rate in Finland and the Nordic countries

In 2017, the fertility rate per woman was 1.49 in Finland (THL, 2018d). This was the lowest rate since the 1970s. However, in the preliminary report for 2018, the decrease in the fertility rate has continued to a figure of 1.40, which will be the lowest rate ever recorded in Finland (Figure 3). The overall fertility rate has decreased in all Nordic countries following a small peak that occurred at the end of 2010. From 2000 to 2010, the fertility rate had increased every year, but after 2010 the rate has decreased in all the Nordic countries. In 2016, the fertility rates for each Nordic country were Sweden 1.85, Iceland 1.8, Norway 1.72, Denmark 1.71, and Finland 1.65. (Worldbank, 2018)

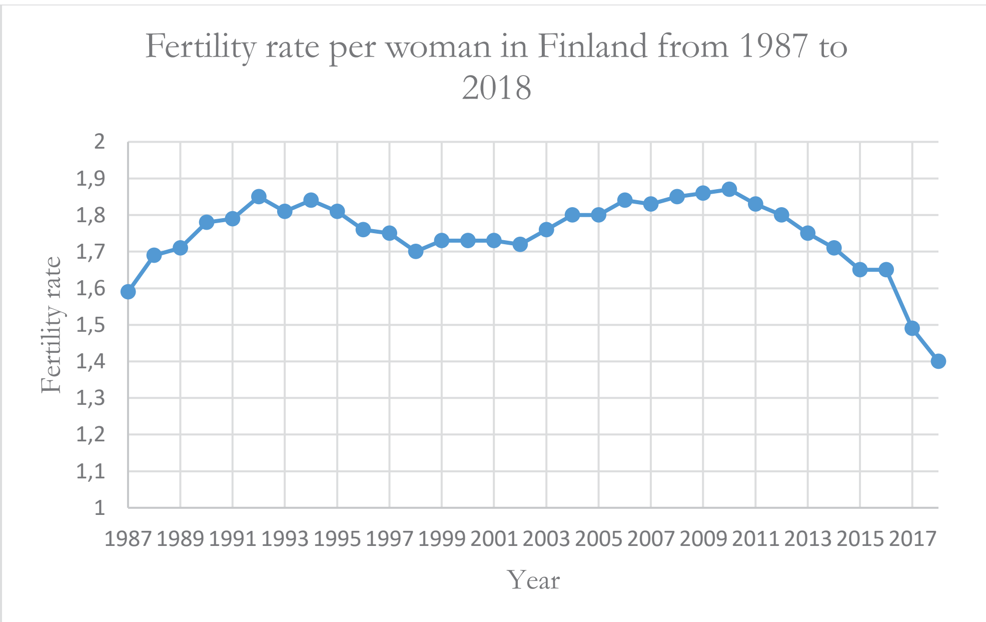


Figure 3. Fertility rate per woman in Finland from 1987 to 2018. The rate for 2018 is based on preliminary results.

2.2.2 Factors decreasing birth rate

Although there are a lot of unknown factors that affect the choice to conceive, certain non-medical conditions are known to affect fertility. According to the findings of a large nationwide questionnaire, the most common reasons for delaying pregnancy among childless 20 to 34 year old men and women in Finland (Perhebarometri 2015) were no permanent partner, child restricting current lifestyle, low income level, young age, and insecure job situation. (Miettinen, 2015)

Socioeconomic status affects birth rate. Historically, the birth rate has first declined in the highest socioeconomic classes before transitioning to the overall population. Eventually, however, the fertility rate has either decreased or increased in all classes. (Dribe et al., 2017) Among young Finnish women, parents who are from a lower socioeconomic class predict a higher fertility rate compared to those from the upper classes (Väisänen & Murphy, 2014). Women with a higher level of education in Finland have a lower fertility rate according to a birth cohort study. The same study also presented that higher parental socioeconomic class and higher standard of living during childhood also led to lower fertility. (Nisén, Myrskylä, Silventoinen, & Martikainen, 2014)

In Finland, women and men with higher levels of income have a higher preferred ideal family size than those who earn less. For example, in the lowest income group, 20% wanted no children at all. (Miettinen, 2015) Interestingly, a nationwide study estimated that a higher minimum wage would decrease fertility among adolescents in the US (Bullinger, 2017). This finding along with the findings of Väisänen & Murphy shows that the fertility pattern among adolescents differs greatly from that of older persons.

Smoking, alcohol, and obesity decrease male fertility (Fullston, McPherson, Zander-Fox, & Lane, 2017). Smoking decreases semen quality and decreases the success rate of fertility treatments (Kovac, Khanna, & Lipshultz, 2015). Women receiving fertility treatments have a significantly lower rate of smoking, which indicates that women having fertility problems are motivated to conceive (Tong et al., 2016). Women who currently smoke have a lower number of children than those who have never smoked or have stopped smoking (Oboni, Marques-Vidal, Bastardot, Vollenweider, & Waeber, 2016).

2.2.3 Chronic diseases and fertility

The prevalence of the most common chronic diseases among fertile-aged women and men in Finland according to the reimbursement statistics of Kela are shown in Table 4 (interactive open access databases of Kela (www.kela.fi) and Tilastokeskus (www.tilastokeskus.fi)). The most common chronic diseases among pregnant women in Finland are asthma, hypothyroidism, epilepsy, RA, and DM. (Artama et al. 2011)

DM especially affects male fertility since it has negative effects on reproductive functions, such as erectile dysfunction due to vascular and neural problems, ejaculatory dysfunction, and hypogonadism. For women, the reproductive problems include hypogonadism, dyspareunia, polycystic ovarian syndrome, and menstrual dysfunction. (Gandhi et al., 2017) A Finnish cohort study analyzed the birth rate in patients with childhood-onset type 1 DM and found that both men and women had a lower probability for offspring. They also presented that younger age at the time of diagnosis decreases fertility (Sjöberg et al., 2013). Fertility rates were analyzed pre and post type 1 DM diagnosis in a Taiwanese study, where a diabetic group had significantly lower rates of live births both before and after diagnosis compared with a reference group (Lin et al., 2018).

RA decreases female fertility (Hargreaves, 1958; Katz, 2006; Skomsvoll, Ostensen, Baste, & Irgens, 2001; Wallenius et al., 2011). Large Scandinavian cohort studies have shown that RA patients have a lower number of births, a longer interpregnancy interval, a shorter reproductive time span, and lower fertility rates compared with women without RA (Skomsvoll et al., 2001; Wallenius et al., 2011). In a retrospective cohort study, time to pregnancy from the start of attempting was over 12 months in 42% of RA patients, which is much higher than the rate (20%) in the general population. Disease activity, the use of NSAIDs, and a prednisone dose over 7.5 mg per day were all risk factors for delayed pregnancy. (Brouwer, Hazes, Laven, & Dolhain, Radboud J. E. M., 2015) The most common reasons for fertility problems among RA patients in a study of 71 cases were unexplained subfertility, anovulation, and male factor. Fertility treatments seemed to be effective for RA patients. (Brouwer, Fleurbaaij, Hazes, Dolhain, Radboud J. E. M., & Laven, 2017)

There is an increasing number of studies suggesting that asthma decreases fertility. A large Danish twin study showed that asthma was an independent risk factor for lower fertility and prolonged time to pregnancy, especially if the asthma was untreated (Gade, Elisabeth J. et al., 2014). A higher proportion of pregnancies involve fertility treatment among asthmatic women than non-asthmatic women

(Vejen Hansen et al., 2019). Asthmatic women also have worse outcomes in fertility treatments than those without asthma (Gade, Elisabeth Juul, Thomsen, Lindenberg, & Backer, 2016).

It has been suggested that hypotyroidism decreases fertility; however, once treated, the fertility should be normal (Mintziori, Kita, Duntas, & Goulis, 2016). A Danish cohort study presented that higher TSH, TPOAb levels, and also mild (sub)clinical hypothyroidism could impair fertility (Anne-Dorthe Feldthusen et al., 2015). The screening and treating of mild hypothyroidism or subclinical hypothyroidism during pregnancy or during the time attempting pregnancy remain under discussion, and further studies are needed to address the role they play (Medenica et al., 2015; Usadi & Merriam, 2016).

Obesity has been shown to adversely affect male and female fertility. Obesity decreases male semen quality by decreasing the sperm count, reducing sperm mobility, and causing DNA damage to the sperm (Jensen et al., 2004; Kort et al., 2006; Martini et al., 2010) In women, obesity causes a chronic low-grade inflammatory state which may lead to endocrine dysfunction and subfertility (Broughton & Moley, 2017; Chandrasekaran & Neal-Perry, 2017). Obese women also have more menstrual dysfunction, delayed conceptions, and a lower rate of successful fertility treatments (Brewer & Balen, 2010; Silvestris, de Pergola, Rosania, & Loverro, 2018).

There are some controversial findings that suggest epilepsy may affect fertility rates. A previous Finnish register-study showed that women with epilepsy had a lower birth rate than women without epilepsy (Artama, M et al., 2004). However, another study suggested that epilepsy does not decrease fertility rates and that patients have a similar time to pregnancy compared with women without epilepsy (Pennell et al., 2018).

Table 4. Prevalence of medical reimbursements for the most common chronic diseases among fertile-aged women (15 to 44 years old) and men (15 to 49 years old) in Finland in 1987,2007, and 2017. Data were gathered from the interactive open access databases of Kela (www.kela.fi) and Tilastokeskus (www.tilastokeskus.fi).

	Women						Men					
	1987		2007		2017		1987		2007		2017	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total	1111385	100.0	985870	100.0	977953	100.0	1312334	100.0	1218428	100.0	1202091	100.0
Any reimbursement	83265	7.49	118830	12.05	155791	15.93	104201	7.94	155652	12.77	200389	16.67
Asthma	12779	1.15	29344	2.98	32421	3.32	13016	0.99	28510	2.34	30944	2.57
Diabetes Mellitus												
Type 1	6033	0.54	8714	0.88	12319	1.26	11208	0.85	17560	1.44	24843	2.07
Type 2	-	-	-	-	12316	1.26	-	-	-	-	24846	2.07
Epilepsy	8545	0.77	9859	1.00	10430	1.07	9807	0.75	12223	1.00	12774	1.06
Hypertension	12735	1.15	9604	0.97	3251	0.33	29513	2.25	25101	2.06	11568	0.96
Hypothyroidism	7009	0.63	9559	0.97	8021	0.82	1528	0.12	2982	0.24	2644	0.22
IBD	1076	0.10	6179	0.63	8749	0.89	1468	0.11	8390	0.69	11990	1.00
Rheumatoid disease	6332	0.57	9545	0.97	13181	1.35	5701	0.43	8344	0.68	10384	0.86
Psychotic disorder	9965	0.90	12412	1.26	12937	1.32	14359	1.09	19289	1.58	19381	1.61

2.2.4 THR and sexual functions

The first discussion on sexual functions after THR was already presented in 1979, when Baldursson et al. contacted 44 married THR patients. Questionnaires revealed that 28 of the 44 patients had sexual problems prior to THR due to hip problems. After THR, 27 patients of the 28 reported that the hip was no longer a problem in terms of their sexual life. (Baldursson & Brattström, 1979) In 1991, this problem was addressed and a guide booklet on intercourse after THR was written. The study revealed that males were faster to return to sexual activities after THR compared with females. The preferred positions for males were bottom and for females sideways on the non-operated hip. (Stern et al., 1991)

In a Korean cohort, the most common concern towards intercourse after THR was the fear of THR dislocation during sex, which led to increased stress levels during sex (Yoon, B. et al., 2013). In later reviews, the supine (bottom/top) position is referred to as the safest coital position after THR (McFadden, 2013). Charbonnier et al. conducted an interesting study where they motion captured 12 of the most common sexual positions and 3D tested them for dislocation and impingement of the hip in a computer model. They found that intensive flexion (over 95 degrees) for women and external rotation (over 40 degrees) for men in a few positions were potentially harmful for the implant (Charbonnier et al., 2014).

Since sexual activity was a problem for 46% of the patients prior to surgery and for only 1% after, THR has resulted in major improvements in sexual life. (Stern et al., 1991). A prospective cohort study has shown that nearly 50% of females under the age of 60 at the time of THR experienced increased intercourse frequency and that more positions were possible after THR than before (Klit et al., 2015). Another study reported similar findings and also suggested that women benefited more from THR regarding sexuality activities than men (Laffosse, Tricoire, Chiron, & Puget, 2008). Wang et al. reported that THR increases male sexual satisfaction but not that of the partners of male patients (Wang, Yue, Liu, & Guo, 2014). In a review where 12 studies were analyzed, the main outcome was that there is moderate evidence that THR improves the sexual quality of life among patients of all ages at the time of THR (Harmsen et al., 2016). Furthermore, the type of implant does not have any impact on sexual activity or functions (Nunley et al., 2015).

In a questionnaire study in England, 55% of hip surgeons estimated that four weeks would be the optimal time to continue intercourses after THR (Wall, Hossain, Ganapathi, & Andrew, 2011). However, surgeons were unlikely to discuss this topic with patients before THR. The most common reason for this was that: "patients don't ask about it", or: "I am not aware of the problem". Experienced surgeons were, however, more likely to discuss the topic with the patient. (Harmsen et al., 2017) In 2017, Issa et al. published their review study on this topic and presented the following results: 44% of THR patients reported improved sexual satisfaction, 27% of the patients reported increased intercourse frequency, and 86% of hip surgeons reported rarely or never discussing sexuality with patients (Issa et al., 2017).

2.3 Induced Abortions

2.3.1 Induced abortions in Finland and elsewhere

In 2017, 9 360 induced abortions (IAs) were performed and registered in Finland. IAs are procedures started by a gynecologist in hospitals in Finland, although the medical IA can and is usually done after evaluation at home. To have a pregnancy ending in IA, a statement from two doctors is required. The abortion rate in 2017 was 8.2 IAs per 1 000 fertile-aged (15-49 year old) females. The overall IA rate has decreased every year and the rate in 2017 was the lowest since 1970. (Figure 4) The highest rate in Finland was among 20 to 24 year olds (14.7/1000), but the rate has decreased from previous reports, and the current rate has decreased by 4.1% in comparison to 2016. Of the women who underwent IAs, 38% had one or more previous IA, and 7.6% had had an IA in 2016. (Raskaudenkeskeytykset - THL 2018)

According to the World Health Organization's statistical report, from 2010 to 2014, Finland had the fifth lowest IA rate. The lowest rate was in Switzerland (5 per 1 000 women aged 15-49). (WHO, 2018) Compared to other Nordic countries, Finland has the lowest IA rate and Sweden has the highest IA rate (17.6 IAs per 1 000 fertile-aged women) (THL, 2017). Worldwide, the IA rate among females aged 15 to 44 was 29 per 1 000 in 2003, which means a total of 42 million IAs. Of those, 48% were unsafe and most of the unsafe IAs occurred in developing countries. Europe has generally the lowest IA rates (12 to 18 per 1 000), except for Eastern Europe that has one of the highest IA rates. In eastern Europe, 105 IAs were performed for every 100 livebirths. (Sedgh, Henshaw, Singh, Ahman, & Shah, 2007) Between 2010 and 2014, the IA rate worldwide was 35 per 1 000 among 15 to 44 year old females. The rate was higher in the developing countries (36 per 1 000) than in the developed countries (27 per 1 000). The present trend is that the IA rate will decrease in developed countries but remain stable in the developing countries. (WHO, 2018)

In 2017, the most common indication for IA in Finland was social reasons (92.5%) followed by termination due to detected / suspected fetal anomaly (3.8%), age over 40 (3.3%), 4 or more previous children (2.4%), and age under 17 (1.9%). Most of the IAs were performed before the 12th gestational week, and of those, 62.2% were early (before 8th gestational week) IAs. At the time of the IA, 51.7% of these women had not previously borne offspring. The most common contraception method among IA patients was condom following no contraception. Most patients planned to have long acting reversible contraception after IA. (Raskaudenkeskeytykset - THL 2018)

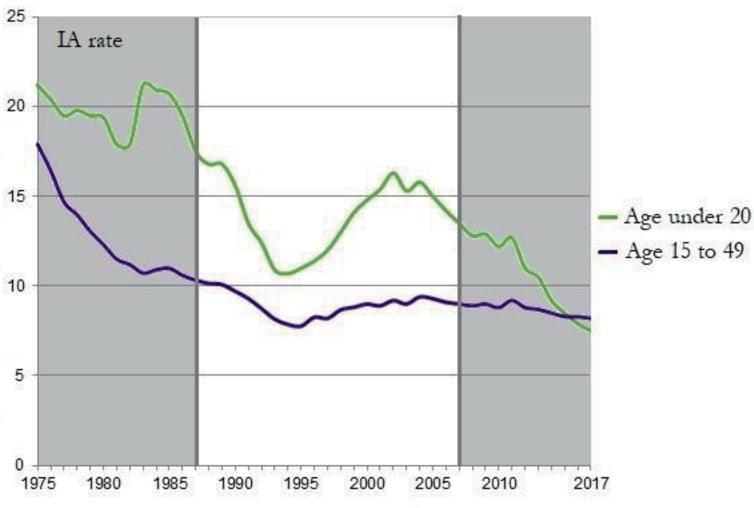


Figure 4. Rate of Induced abortions (IA) per 1 000 similar-aged women in Finland from 1975 to 2017. Our study period (1987 to 2007) highlighted with white background.

Modified from the original publication: THL statistical report, Induced Abortions 2017, https://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/raskaudenkeskeytykset/raskaudenkeskeytykset

2.3.2 Risk factors for pregnancy ending in induced abortion

There are a few known risk factors for pregnancy ending in IA. One of the most common risks is unintended pregnancy, which leads to IA in 56% of pregnancies. Although the rate of unintended pregnancies has decreased, especially in developed countries, the proportion of those ending in IA has remained the same (WHO, 2018).

Young age (under 19) has been shown to be a high-risk factor for IA (Rasch et al., 2008). Teenagers in lower socioeconomic class were more likely to become pregnant and have an IA compared with those in higher socioeconomic classes in a Finnish birth cohort study (Väisänen & Murphy, 2014). In their study, Leppälahti et al. reported that repeat IAs among teenagers increased by 95% (18-19 years old) and 120% (16-17 years old) in Finland between 1993 and 2009 (Leppälahti, Gissler, Mentula, & Heikinheimo, 2012). First intercourse before the 18th birthday was a risk factor for later IA in a Russian / Estonian / Finnish population comparison study (Regushevskaya et al., 2009).

Socioeconomic status has a major impact on pregnancy ending in IA or delivery. According to a Danish study, the highest risk factor for pregnancy ending in IA is single-status. Unemployment and student status also increased the risk for IA, mainly due to lower income level (Rasch et al., 2008). Lower income compared to higher income increases the risk for IA. (Jones, Darroch, & Henshaw, 2002) In Finland, women with basic level education had a higher IA risk compared with women who had higher educational levels (Väisänen, 2015). A low level of education was also a risk factor for repeat IA (Väisänen, 2016).

Other risk factors for repeat IA, according to another Finnish cohort study, are parity and previous IA. However, age over 25 and intrauterine contraception are decreasing the risk factors for IA. (Heikinheimo, Gissler, & Suhonen, 2009) The immediate initiation of contraception after IA reduces the rate of repeat IA, and intrauterine contraception is the most effective in reducing repeat IA (Heikinheimo, Gissler, & Suhonen, 2008). The benefits of intrauterine contraception implanted immediately after IA were supported in a RCT, where the study group received intrauterine contraception and had significantly fewer numbers of IAs during the follow-up (Pohjoranta, Mentula, Gissler, Suhonen, & Heikinheimo, 2015). Short time from previous delivery is also a risk factor for IA, and therefore family planning should also be provided after delivery (Vikat, Kosunen, & Rimpela, 2002). It can be therefore concluded that short interpregnancy intervals should be avoided.

The use of contraception in the Nordic countries is relatively easy due to liberal attitudes towards reproduction. Hognert et al. presented in their study that lower contraceptive use among 20 to 24 year olds in Sweden resulted in higher IA rates compared with Denmark and Norway. (Hognert et al., 2017) The same was seen in an earlier postal survey study, where insufficient use of contraception was suggested to be the reason for high IA rates (Regushevskaya et al., 2009). In Finland, many cities provide free contraception for women aged under 25, since they are at the highest risk, and contraception decreases the IA rate (Gyllenberg, Saloranta, But, Gissler, & Heikinheimo, 2018) as well as being cost-effective (Cleland, Peipert, Westhoff, Spear, & Trussell, 2011).

2.3.3 Chronic diseases and induced abortion

No studies have been carried out on THR patients' risk of pregnancy ending in IA. A major proportion (20 to 49%) of young THR patients suffer from RA (see chapter 2.1.2.2), and therefore chronic diseases were taken as part of this present study, since chronic diseases have been shown to affect reproduction. The impact of RA on reproduction is mainly due to the medications used to treat the disease. For example, methotrexate increases the risk for congenital malformations. However, Vinet et al. compared the rate of induced abortions among RA patients using methotrexate with patients using biological medications. The results of the study showed that methotrexate users had a lower rate of IAs. Moreover, the overall IA rate among RA patients was similar to national levels in this study. (Vinet, E., Kuriya, Pineau, Clarke, & Bernatsky, 2013)

Women with asthma have a higher risk for spontaneous abortion, but not for IA generally. Women with uncontrolled asthma have a higher risk for both spontaneous and induced abortion. (Blais et al., 2013) One smaller previous study showed that severe asthma would increase IA rates (Tata et al., 2007).

A few studies have discussed IA in patients with diabetes mellitus (DM). A Danish study reported that IA was not more common among women with DM (Kjaer et al., 1992). However, another Danish study suggested that patients with type 1 DM had increased rates of spontaneous and induced abortions (Lorenzen, Pociot, Johannesen, Kristiansen, & Nerup, 1999). An Italian prospective cohort study showed no increase in spontaneous or induced abortions among women with either type 1 or type 2 DM (Lapolla et al., 2008)

A recent study reported that chronic diseases were not risk factors for complications in uterine evacuation IA compared with women without comorbidities. Furthermore, there was no evidence to suggest that any specific comorbidity would increase the complication risk either. Therefore, the authors concluded that surgical IA is safe among women with chronic diseases (Guiahi, Schiller, Sheeder, & Teal, 2015)

2.4 Pregnancy and delivery

2.4.1 Pregnancies and deliveries in Finland

In 2017, there were 50 151 deliveries in Finland of which 99.5% occurred in hospitals. Outside hospital deliveries have increased because the number of delivery hospitals has been reduced. In 1991, there were 49 delivery hospitals but only 25 remained in 2017. Furthermore, 7 of the 25 did not fulfil the criteria for delivery hospitals of a minimum 1 000 deliveries per year. Of the total outside hospital deliveries, 93 deliveries occurred on the way to hospital and an additional 87 were otherwise unplanned outside hospital births. (THL, 2018d)

The mean age at delivery was 30.9 years for all deliveries and 29.2 for primiparas. In recent years, parturient age has increased in all Nordic countries. The mean BMI before the pregnancy was 24.8. Over a third of parturients were overweight. Gestational diabetes was diagnosed for 16% of women during pregnancy. In Finland, smoking during pregnancy has decreased in recent years, and in 2017 only 12.5% of women smoked during early pregnancy. Similar trends can be seen in all Nordic countries. (THL, 2018d; THL, 2018f)

The overall proportion of caesarean sections (CS) has been 16 to 17% for the past 20 years. However, only 5% are emergency sections. CS is more common among older (over 35 years of age) primipara women. During delivery, the most common analgesia used were nitrous oxide (53.5%), epidural (50%,) and spinal (20%). Non-pharmaceutical pain relief was common, and almost 40% of the women used it. Only 7.8 % of women did not use any analgesia during delivery. (THL, 2018d)

2.4.2 Delivery methods, briefly

The most common vaginal delivery position is the “supine” position in which the woman lays on her back on the delivery table and the legs are rested in flexion position to gain better push and angle to the pelvis. However, there are plenty of possible vaginal delivery positions including either lying down or upright positions. There are RCTs and a Cochrane review that suggest upright positions are equally as safe to the lying down positions (Gupta, Sood, Hofmeyr, & Vogel, 2017; Thies-Lagergren, Kvist, Christensson, & Hildingsson, 2011; Thies-Lagergren, Kvist, Christensson, & Hildingsson, 2012; Zhang et al., 2017). Moreover, the upright positions may reduce perineal traumas and the delivery can be faster requiring less assistance, but they may also lead to higher blood loss (Gupta et al., 2017).

CS can be divided into planned and unplanned. The most common reasons for elective CS are abnormal fetal positions, small pelvis, previous CS, early preeclampsia, and the fear of vaginal delivery. The most common indications for unplanned emergency CS are fetal bradycardia, umbilical cord prolapse, and placental ablation. The goal of emergency CS is to have the neonate born within 10 minutes after the CS decision has been made. Therefore, emergency CS is done under general anesthesia, whereas planned CS is performed under regional anesthesia. (Tapnainen, Heikinheimo, & Mäkikallio, 2019) Planned CS is usually performed by horizontal incisions (Phannenstiel or Joel-Cohen). Emergency CS is done vertically. (Salo, H., Tekay, & Mäkikallio, 2015)

2.4.3 Chronic diseases and pregnancy / delivery

The most common long-term diseases among fertile-aged women in Finland are presented in Table 3. The diseases with the highest prevalence are Asthma, DM, rheumatoid diseases, and major psychiatric diseases. The most common long-term diseases among pregnant women in Finland, according to a previous study, are asthma, hypothyroidism, epilepsy, RA, and DM. (Artama, Miia et al., 2011). In a German population-based study, the highest prevalence was recorded for allergies, metabolic disorders, asthma, chronic nervous diseases, and chronic skin diseases. This study concluded that women with any chronic disease have a higher risk for adverse pregnancy outcome than those with non-chronic diseases (Kersten et al., 2014).

There are only a few chronic diseases in which the pregnancy is contraindicated due to an increased risk of death during pregnancy. Mostly, these diseases are heart diseases which may greatly increase maternal mortality during pregnancy, delivery, and postpartum care (Siu & Colman, 2001). For example, maternal mortality has been 30 to 50% in pulmonary vascular diseases (Weiss & Hess, 2000).

In one third of asthmatic women, the symptoms get worse during pregnancy, for one third the symptoms remain the same, and one third have fewer symptoms (Schatz et al., 1988). Asthma increases the risk for hypertension during pregnancy, preterm delivery, and CS (Källén, Rydhstroem, & Aberg, 2000; Murphy, Vanessa E., Jensen, & Gibson, 2017; Shaked, Wainstock, Sheiner, & Walfisch, 2019). A nationwide Swedish cohort study found that asthmatic women have a higher risk for preeclampsia, premature labor, and placental abruption (Rejnö et al., 2014). Asthma exacerbations during pregnancy are associated with higher adverse pregnancy outcomes (Ali, Hansen, & Ulrik, 2016).

Pregestational DM increases risk related to pregnancy and delivery. There is no difference in risk for pregnancy between type 1 and type 2 DM mothers. (Sato et al., 2014) However, women with pregestational DM have a higher risk for CS (Berger et al., 2016; Ehrenberg, Durnwald, Catalano, & Mercer, 2004). PDM increases the risk for hypertensive pregnancy disorders and preeclampsia (Berger et al., 2016; Sibai, B. M. et al., 2000; Sibai, Baha M., 2002).

Rheumatoid diseases do not substantially increase the risk for adverse pregnancy outcomes, and RA symptoms are relieved in the majority of the women during pregnancy (Nelson & Ostensen, 1997). However, women with RA have higher rates of CS than women without RA (Aljary, Czuzoj-Shulman, Spence, & Abenhaim, 2018; Bowden, Barrett, Fallow, & Silman, 2001; Wallenius, Salvesen, Daltveit, & Skomsvoll, 2014). Women with RA have a higher risk for preeclampsia and hypertension during pregnancy (Aljary et al., 2018; Wallenius et al., 2014).

Maternal pre-pregnancy obesity increases the risks relating to pregnancy and delivery (Marchi, Berg, Dencker, Olander, & Begley, 2015). Obese women have higher risks for gestational hypertension, preeclampsia, GDM, and CS delivery (Gaillard et al., 2013; Vernini et al., 2016; Vinturache, Moledina, McDonald, Slater, & Tough, 2014). Obesity increases the risk for induced deliveries and emergency CS (Reiss et al., 2016; Vinturache et al., 2014). Obesity also increases the risk for complications after CS (Vegel, Benden, Borgert, Kallies, & Kothari, 2017).

Epilepsy increases the risk for adverse pregnancy outcomes. Epileptic women also have a higher risk for CS delivery (Artama, Miia et al., 2017; Razaz, Tomson, Wikström, & Cnattingius, 2017; Viale et al., 2015) and are more likely to have preeclampsia, hypertension, placental problems, infections, and ante/postpartum hemorrhage (Razaz et al., 2017; Viale et al., 2015).

2.4.4 Delivery after THR

The first case reports on delivery and pregnancy after THR were published already in the 1970s and 80s. These reports reported successful pregnancies and deliveries among women with THR, where THR did not affect delivery or pregnancies. (Monaghan, Lenehan, Stronge, & Gallagher, 1987; Reckling, 1976; Wittich, 1982) In the 1990s, Ostensen described the first problems with deliveries after THR. In a case series of eight women who underwent THR due to RA, all eight deliveries were CS due to the concern that vaginal delivery could adversely affect implant survivorship. (Ostensen, 1993) In later studies, Meldrum et al. (2003) presented a lower CS proportion than Ostensen, but four of the eight CS deliveries were performed due to the patients fear of vaginal delivery harming the THR. Additionally, Stea et al. (2007) had a 92.9% CS proportion in their case series. Of the 14 deliveries, 13 were CS. The CS deliveries were performed because of the preferences of obstetricians for planned cesareans due to THR. Furthermore, the authors explain the higher CS rate by the country's higher CS rate compared to those in previous studies, and that women with developmental dysplasia of the hip have reduced pelvic size. (Stea et al., 2007)

Lower CS rates were presented in a majority of the previous studies. Yazici et al. presented 20 deliveries and six of those were CS. Moreover, they concluded that THR does not have an impact on pregnancy and delivery. (Yazici et al., 2003) By far the largest study on this topic also had similar rates of CS after THR to national levels. Sierra et al. (2005) had 47 singleton deliveries in their retrospective case series and 17 of those were CS. They concluded by stating that THR does not seem to adversely affect pregnancy or delivery. (Sierra et al., 2005) Yoon et al. reported similar findings to these previous studies in their case series of 16 deliveries and seven CS (Yoon, H. J. et al., 2012). However, none of the previous studies have had a reference group. Hence, all the pregnancy and delivery results have been compared to national statistics.

The latest study (Lally et al., 2015) was the first to compare pre-THR and post-THR pregnancies and deliveries. However, in their study, no reference group without THR is presented. The study suggested that THR does not affect pregnancy or delivery method compared with pre-THR pregnancies. (Lally et al., 2015) In all of the previous studies, the CS proportion among women with THR has been higher compared with Finnish standards, even though vaginal deliveries after THR have been stated to be safe. The results of the previous studies are summarized in Table 5.

Table 5. Most important previous studies of pregnancy outcomes and delivery methods after maternal THR

Author	Study period	Study design	No. of patients	No. of hips	No. of deliveries	No. of CS (%)	Results	Comment
Reckling et al. (1976)		Case report	1	1	1	-	Normal pregnancy and delivery	
Wittich (1982)		Case report	1	1	1	-	Normal pregnancy and delivery	
Monaghan et al. (1987)		Case report	1	1	1	-	Normal pregnancy and delivery	
Ostensen (1993)		Case series	8	8	8	8 (100)	All of the deliveries were CS due to fear of vaginal delivery causing harm to THR	
Yazici et al. (2003)	1981-1988	Case series	20	20	20	6 (30.0)	No adverse pregnancy outcomes	No reference group
Meldrum et al. (2003)	1981-2000	Case series	13	20	19	8 (42.1)	No effect on neonates but 4/13 women delivered by CS due to fear of vaginal delivery harming THR	No reference group
Sierra et al. (2005)	1975-1995	Case series	47	52	47	17 (36.2)	No adverse pregnancy outcomes, no impact on delivery method	No reference group
Stea et al. (2006)	1990-2005	Case series	14	14	14	13 (92.9)	No adverse pregnancy outcomes. Increased rate of CS	Only previous study to report birth weights
Yoon et al. (2012)	1997-2000	Case series	11	16	16	7 (43.8)	No adverse pregnancy outcomes, no impact on delivery method	No reference group
Lally et al. (2015)	2007-2011	Cohort	10	10	10	3 (30.0)	After THR, pregnancies were similar to those before THR	Only study to report also pre THR pregnancies

2.5 Neonates

2.5.1 Neonates in Finland

In 2017, 50 854 neonates were born in Finland. Of these, 50 710 (99.7%) were born alive and only 144 were stillbirths. Most of the neonates (99.5%) were born in hospital. The perinatal death rate (comprising those born dead or died during first week after delivery) in 1987 was 8.7 / 1 000 births. This figure decreased to 5.9 / 1 000 births in the early 2000s and 3.9 / 1 000 births in 2017. The rate of preterm birth has also decreased in recent years and 5.3% of births were preterm. The rate of low-birth-weight (LBW) (4.3%) and very-LBW neonates (0.7%) has remained stable. Mean birth-weight was 3 554 grams for boys and 3 439 grams for girls. At the age of one week, 93.5% of the neonates were at home in 2017, whereas the proportion in 1987 was only 75.9%. (THL, 2018d)

2.5.2 Maternal chronic diseases and neonate birth outcome

Maternal obesity increases the risks for intrauterine growth restriction and SGA infants, but also for LGA infants. Obesity also increases the risk for preterm delivery due to obesity related pregnancy complications. (Chandrasekaran & Neal-Perry, 2017; McDonald, Han, Mulla, & Beyene, 2010; Torloni et al., 2009) Obesity increases the risk for LGA infants and the risk for childhood obesity (Gaillard et al., 2013). Children born to obese mothers had later hospital discharge after delivery compared with non-obese mothers (Vernini et al., 2016). Obese women also have a higher risk for stillbirth and fetal death (Aune, Saugstad, Henriksen, & Tonstad, 2014; Flenady et al., 2011). Obese mothers are also less likely to breastfeed and to quit breastfeeding earlier (Turcksin, Bel, Galjaard, & Devlieger, 2014).

Maternal asthma is an increased risk for preterm delivery but not for adverse neonatal outcomes, according to a large Israeli cohort study (Shaked et al., 2019). An older Swedish register study showed that women hospitalized due to asthma before pregnancy had a higher risk for stillbirth than those without asthma (Källén et al., 2000). A Canadian population-based register study found that maternal asthma increased the risk for perinatal mortality, mainly because more of these neonates were preterm and SGA (Breton et al., 2009). Neonates born to mothers with asthma had a higher risk for infant hypoglycemia (Ali et al., 2016; Källén et al., 2000).

Maternal pregestational DM increases the risk for adverse neonatal outcomes. The perinatal mortality rate, for example, is increased by up to five-fold compared with non-diabetic pregnancies (Colstrup, Mathiesen, Damm, Jensen, & Ringholm, 2013; Eidem, I. et al., 2011; Galindo, Burguillo, Azriel, & Fuente, 2006; Lauenborg et al., 2003; Mathiesen, Ringholm, & Damm, 2011). Neonates with maternal pregestational DM are more likely to be born preterm and to be SGA or LGA compared with neonates without maternal pregestational DM. (Colstrup et al., 2013; Eidem, I. et al., 2011; Macintosh et al., 2006; Sibai, B. M. et al., 2000). These adverse events can be minimized with good preconception care and optimal glycemic control, which requires adjustments during pregnancy (Sugrue & Zera, 2018).

A previous study reported that neonates born to mothers with active RA during pregnancy had significantly lower birthweight that those with RA in remission or with no RA (Bowden et al., 2001). Another study found that neonates were more likely to be born preterm and that RA activity during pregnancy did not have an impact on this finding, with 28% of the neonates born preterm (Langen, Chakravarty, Liaquat, El-Sayed, & Druzin, 2014). Larger cohort studies have also confirmed the finding of an increased risk for preterm birth and SGA (Aljary et al., 2018; J.F Skomsvoll, V Baste, M Østensen, L.M Irgens, 1999; Wallenius et al., 2014). Stillbirth and neonatal death rates are not, however, increased in RA pregnancies (Aljary et al., 2018; Eudy, McDaniel, & Clowse, 2018; J.F Skomsvoll, V Baste, M Østensen, L.M Irgens, 1999; Wallenius et al., 2014)

Pregnancies complicated by epilepsy have a higher risk for adverse neonatal outcome (Soontornpun, Choovanichvong, & Tongsong, 2018). Indeed, in a Finnish cohort study, maternal epilepsy increased the risk for SGA neonate, admission to neonatal intensive care unit, and need for respiratory care (Artama, Miia et al., 2017). In addition, a Swedish cohort study showed an increased risk for stillbirth, SGA, neonatal infections, preterm birth, asphyxia, low Apgar scores, and hypoglycemia (Razaz et al., 2017).

2.5.3 Maternal THR and neonates

The first reports on healthy neonates born to mothers with THR were published in the 1970s and 1980s. Three case reports described successful births with healthy neonates after maternal THR. (Monaghan et al., 1987; Reckling, 1976; Wittich, 1982) Ostensen (1993) published the first case series in which eight healthy neonates were born by CS for mothers with THR due to RA.

Since then, five more case series and one cohort study have investigated neonates after THR. Yazici et al. (2003) only reported that 20 healthy neonates were born between 1981 and 1988 in their case series and provided less precise information than the other studies. Meldrum et al. reported 20 pregnancies with 19 deliveries from 1981 to 2000 in their series. There was one emergency CS due to the transposition of the child in the uterus that did not affect the neonate outcome. One neonate suffered from Rh immunization, but overall the THR seemed to not affect neonate outcome. (Meldrum et al., 2003) The largest previous study, with 47 pregnancies, focused mainly on delivery method and prosthesis survival. The authors state that all of the 47 pregnancies had successful outcome, which indicates that all the neonates were born healthy.

Stea et al. were the first to report more specific results of the neonates born after maternal THR. They reported 14 successful livebirths. Of the 19 deliveries, only one was preterm and no adverse birth outcomes were detected. The mean birthweight and height did not differ from the national means. Breastfeeding was successful among all the mothers who wanted to breastfeed. (Stea et al., 2007)

None of these previous studies had a reference group. Furthermore, only one study compared pre- and post-THR pregnancy outcomes. Ten pregnancies occurred after THR and 82 before THR. Nine singletons and one pair of twins were born and all of them were reported to be healthy. The mean birthweight did not differ from the national means. One of the deliveries was classified as complicated, but the outcome was not adverse. (Lally et al., 2015)

2.6 Congenital anomalies

2.6.1 Congenital anomalies in Finland

In 2014, 2 822 major congenital anomalies were diagnosed in Finland. The rate of major congenital anomalies was 546/10 000 live or stillborn neonates. The rate has been stable for the past few years. Termination of pregnancy was preformed due to detected fetal anomaly in 357 pregnancies. Of the liveborn neonates, 4.9% had major congenital anomalies, and 17.6% of the stillborn neonates had one or more major anomaly. (THL, 2018a)

The most common anomalies in Finland in the 21st century have been trisomy 21 (27.6 cases per 10 000 neonates), cleft palate (15.0), limb reduction defect (12.3), cleft lip without or with cleft palate (10.8), and coarctation of the aorta (10.3). Some anomalies are more lethal than others. A high percentage of the following anomalies lead to stillbirth: anencephaly (42.3% were stillbirths out of all births with this anomaly), trisomy 18 (36.0%), bilateral renal agenesis (23.5%), and trisomy 13 (16.1%). The proportions of infantile deaths out of all births with the anomaly for the most lethal anomalies in Finland were as follows: anencephaly (100.0%), bilateral renal agenesis (94.9%), trisomy 13 (91.5 %), trisomy 18 (85.7%), and hypoplasia of left heart syndrome (45.5 %). (THL, 2018a)

In Finland, women are screened for congenital anomalies during pregnancy. Three screening options are available for families. The first is to not participate in any of the screenings, which are voluntary. The second is to participate in ultrasonography screening, but not in chromosomal screening, in which the ultrasound is performed in gestational weeks 10+0-13+6. The third and the best option is to participate in both the ultrasound and chromosomal screening. In gestational weeks 9+0-11+6, a blood serum sample for chromosomal risks is taken, and then in gestational weeks 11+0-13+6 ultrasound in performed. Then, the results of these are combined to calculate the individual risk for the most common chromosomal disorders (trisomies, 21,18 and 13). (Leipälä, Ignatius, Autti-Rämö, & Mäkelä, 2009). Each hospital district and town is obligated by the state law on screenings (339/2011) to provide these screenings for every pregnant woman, but each of them has its own particular practices for the screenings.

2.6.2 Chronic diseases and congenital anomalies

Many chronic diseases have an increased risk for congenital anomalies in offspring. All drugs are tested for malformation risk and classified according to the perceived risk. In Finland, Medbase Oy maintains the GravBase database as part of the Terveysportti services. It contains over 1 100 drugs and information on their impact on the fetus.

There have been controversial findings as to whether RA increases the risk for congenital anomalies. Some studies suggest that RA could increase the risk compared with non-RA pregnancies (J.F Skomsvoll, V Baste, M Østensen, L.M Irgens, 1999; Nørgaard et al., 2010). A larger Norwegian register study compared RA pregnancies with non-RA pregnancies but found no increase in risk for congenital anomalies (Wallenius et al., 2014). In Finland, RA patients are given reproductive counseling since some of the drugs commonly used to treat RA are prohibited for use not only during pregnancy and lactation but also for months prior to pregnancy (Sihvonen & Pertovaara, 2019).

DM types 1 and 2 have been shown to increase the risk for congenital anomalies (Eidem, Ingvild et al., 2010; Macintosh et al., 2006). Gestational diabetes also increases the risk, but less than pregestational diabetes (Sheffield, Butler-Koster, Casey, McIntire, & Leveno, 2002; Zhao, Zhang, Zeng, & Liu, 2015). The risk for congenital heart anomalies is increased, especially if there is history of diabetic complications (Øyen et al., 2016). The most common anomalies in the offspring of insulin-dependent diabetic mothers were neural tube defects, heart defects, and bilateral renal agenesis (Becerra, Khoury, Cordero, & Erickson, 1990; Nasri, Houde Ng, Westgate, Hunt, & Holmes, 2018).

Chronic hypertension is an independent risk factor for congenital anomalies, whether it is treated or untreated (Bateman et al., 2015). Asthma also increases the risk for certain congenital anomalies, although researchers have not been able to conclude whether the drugs used to treat asthma or the disease itself increases the risk for congenital anomalies. (Garne et al., 2015; Murphy, V. E. et al., 2013) Certain drugs used to treat diseases, such as epilepsy and depression, have been shown to increase the risk for congenital malformations, although the diseases themselves are not thought to increase the risk. (Artama, M., Auvinen, Raudaskoski, Isojärvi, & Isojärvi, 2005; Bromley, Weston, & Marson, 2017; Malm, Artama, Gissler, & Ritvanen, 2011; Weston et al., 2016)

Maternal obesity increases the risk for certain congenital anomalies. In particular, the risk for neural tube defect, spina bifida, and cardiovascular anomalies is increased. Overall, the absolute increase was concluded to be small in this meta-analysis. (Stothard, Tennant, Bell, & Rankin, 2009) However, another cohort study suggested that the overall risk for congenital anomalies increased in both obese and underweight women compared with women of a recommended weight (Rankin et al., 2010).

3 AIMS OF THE STUDY

The overall aim of the present study was to provide important nationwide information on reproductive health of fertile-aged THR patients.

The specific aims of the studies were to investigate the following:

1. Birth rates after THR performed for fertile-aged males and females compared with a reference group without THR.
2. The risk for pregnancy ending in IA after THR compared with preoperative pregnancies and a reference group without THR.
3. The safety of pregnancy and delivery, the delivery method, and neonate outcomes compared between the THR patient group and reference group both before and after THR / index date.
4. The risk for congenital anomalies in the offspring of women who had undergone THR compared with a reference group. Further, to compare the risk of congenital anomalies between women with MoM THR-implants with non-MoM implants in a subgroup analysis.
5. The survival of primary THR after pregnancy and delivery in comparison with a reference group of women with THR without deliveries and to compare revision indications between groups.

4 METHODS AND PATIENTS

4.1 Study design

This nationwide retrospectively formed register-based cohort study contained information from six different national registers in Finland. The registers used in this study were the following: the Finnish Arthroplasty Register (FAR), the Population Information System (PIS), the Medical Birth Register (MBR), the Register of Induced Abortions (RIA), the Register of Congenital Malformations (RCM), and the Register of Medical Reimbursements (RMR). All the information gathered from the registers was combined by using the unique social security code of each person selected for the study. The whole study period was from the 1st of January 1980 to 26th of January 2011.

4.2 Registers

Finland has a long history of personal registers. The first personal registers were established in the 16th century, and the first personal health registers during the 20th century. Personal health registers are designed to improve the quality of healthcare and to provide data for national statistics and research. (Statistics Finland, 2018)

Finnish legislation the Personal Data Act (523/1999) and the Act on National Personal Data Registers kept under the Health Care System (556/1989) enables the registers to be maintained and used for research purposes and allows the use of confidential data in research without the need for the written consent of the participants when register data only are used. This legislation obligates hospitals to collect the required information and to report it to the registers.

The new European General Data Protection Regulation (GDPR) (GDPR 2016/679) came into effect on the 25th of May 2016, and the member states of the European Union (EU) started to enact the GDPR on the 25th of May 2018. On the 1st of January, the Data Protection Act (1050/2018) replaced the old Finnish

Personal Data Act. The Data Protection Act is set to complement and clarify the GDPR in Finland. Our study permissions were granted before the GDPR came into force and were therefore based on the old standards of the Personal Data Act (523/1999). The new Data Protection Act (1050/2018) enables the continued use of register data for scientific research in Finland.

4.2.1 The Finnish Arthroplasty Register

The Finnish Arthroplasty Register (FAR) is maintained by the National Institute of Health and Welfare (THL). The FAR contains information on all prostheses operated since 1980. The following information was gathered from the register and used in this study: the date of the surgery, THR indication, age at the time of THR, implant type and materials, date of possible revision, number of revisions, and revision indications. All females aged between 15 and 45 at the time of the operation and operated between 1980 and 2007 were selected for the study. For the first part of the study, all males aged 15 to 49 at the time of the operation and operated from 1980 to 2007 were selected. Information on all the prostheses operated for one person during the study period was gathered. The current (2017) completeness of the FAR for primary THR is 95%, and it matches well with the hospital discharge data. For revision THR, the completeness of the FAR is slightly lower at 81%. (THL, 2018c) During our study period the completeness was 90% in 1995 and 95% in 2000 (Puolakka T et al 2001). During the study period, information on prosthesis operations was gathered from paper forms filled-out by surgeons and sent to THL. The FAR has undergone major improvements. At the end of 2015, the whole register was totally renewed and completely digitalized to match current standards. The FAR provides interactive and updated reports on their website: thl.fi/far.

4.2.2 Population Information System

The Finnish Population Information System (PIS) is maintained by the Population Register Centre of Finland. The first population registers were created in the 16th century in Finland. The PIS contains information on all permanent residents in Finland. The following personal data are gathered in the register: name, personal identity code, citizenship, native language, family relations, date of birth, and death. (Population Register Centre, 2019). The contents of the PIS are made available for research in accordance with the Population Information Act (661/2009).

From the PIS, three reference persons for each study patient were selected. The referents were matched by age, gender, and native language, and they had no implants according to FAR. Further, dates of emigration and death were gathered from the PIS for each participant. For the first part of the study, information on all the biological children born was gathered from the PIS because information on the offspring of males is not included in the Medical Birth Register (MBR). The common closing date for the information on the children born was the 26th of January 2011.

4.2.3 Medical Birth Register

The MBR is a nationwide mandatory register maintained by THL. Furthermore, the MBR contains information on all pregnancies, deliveries and neonates up to seven days postpartum in all pregnancies that had lasted for over 22+0 gestational weeks or fetuses weighing over 500 grams at birth. The MBR was established in 1987, and since then, it has been renewed in 1990, 1996, 2004, and 2017. The goal of the register is to collect data for statistics and research and to develop reproductive health in Finland. The current coverage of the register is nearly 100%. (THL, 2018e)

In this study, we collected all the live and stillbirths recorded in the MBR for women from both the THR and reference groups from 1987 to 2007. For this study, we used all the available variables that were in the MBR during the study period. The most important missing variables were the lack of delivery durations as well as the lack of 5-minute Apgar points and maternal BMI before pregnancy, since they only became part of the register in 2004. Also, the coding for CS was two-parted (planned or other) instead of the current coding (planned, urgent, emergency). The MBR uses electronic reporting from the delivery hospitals, and in planned home deliveries the midwives assisting the delivery report the births to the register. An up-to-date list of the information recorded to the MBR can be found on the homepage of the MBR (https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/newborns).

4.2.4 Register of Induced Abortions

The Register of Induced Abortions (RIA) is maintained by THL, and it is one of the mandatory health registers in Finland. The RIA was first established in 1983, but information on the numbers and indications of IA is available from 1955. The aim of the register is to provide data for statistics and research. (THL, 2018g). The completeness of the register in 2011 was excellent 97% (Heino, Niinimäki, Mentula, & Gissler, 2018). Since 2015, information has been gathered electronically from hospitals. During our study period, the information was provided using paper forms filled-out by the performing physicians and mailed by the hospitals to THL.

For our study, information on all IAs from 1987 to 2007 was gathered for both THR patients and the reference group. The variables used in this study were the following: number of IAs during study period, previous IAs at the time of current IA, date of the IA, age at the time of IA, indication of IA, SES of women, and number of previous pregnancies and deliveries. Up-to-date information on the content recorded to the RIA can be found from the homepage of the RIA. (https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/register-of-induced-abortions)

4.2.5 Register of Congenital Malformations

The Register of Congenital Malformations (RCM) was established in 1963 and is now maintained by THL. The main goal of the RCM is to provide actual information on nationwide anomalies and to help detect possible new teratogens and prevent major anomalies by providing information on current rates. The RCM has information on all pregnancies ending in livebirth or stillbirth where the fetus has one or more major anomalies. Information on the terminations of pregnancies due to detected or suspected fetal anomaly (TOPFA) is also recorded to the register. Anomalies are usually recorded to the register during the first year after birth. Every year, over 2000 major anomalies are reported to the register. (THL, 2018b) Anomalies categorized as major were included for this part of the study. Major anomalies include those severe anomalies and chromosomal diseases that either demand surgical treatment or seriously affect everyday life. All the anomaly diagnoses and categorization to major or minor were checked manually, and diagnoses were classified and grouped using the International Classification of Disease, version 10 (ICD-10).

4.2.6 Register for Medical Reimbursement

The Register for Medical Reimbursement (RMR) is maintained by Kela. The Health Insurance Act (1224/2004) grants Kela the right to maintain this register. The register holds information on all reimbursable diseases and their medications. Kela has three categories of reimbursements at the moment: Basic (40% of the expenses), Lower special (65%), and Higher special (100%). For the special categories, a medical certificate issued by a doctor on form B is required to gain entitlement for the reimbursement of medication expenses. (Kela, 2018) In this study, we gathered all the reimbursements due to chronic diseases registered to the RMR before the 26th of January 2011 for the whole study population to gain information on their long-term diseases. If no record of reimbursements for medical costs was found in the RMR, the person was classified as not having the disease. Information on medical drug purchases was not obtained for this study.

4.3 Patients

Information on a total of 2 429 women and 3 434 men who underwent THR surgery between 1980 and 2007 were obtained from the FAR. The reference group comprised 7 276 women and 10 299 men that had no implants according to the FAR and were matched by age, hometown, and mother tongue. Due to missing data and inclusion restrictions, participant numbers differ between studies I to V, and are therefore described in detail in following chapters.

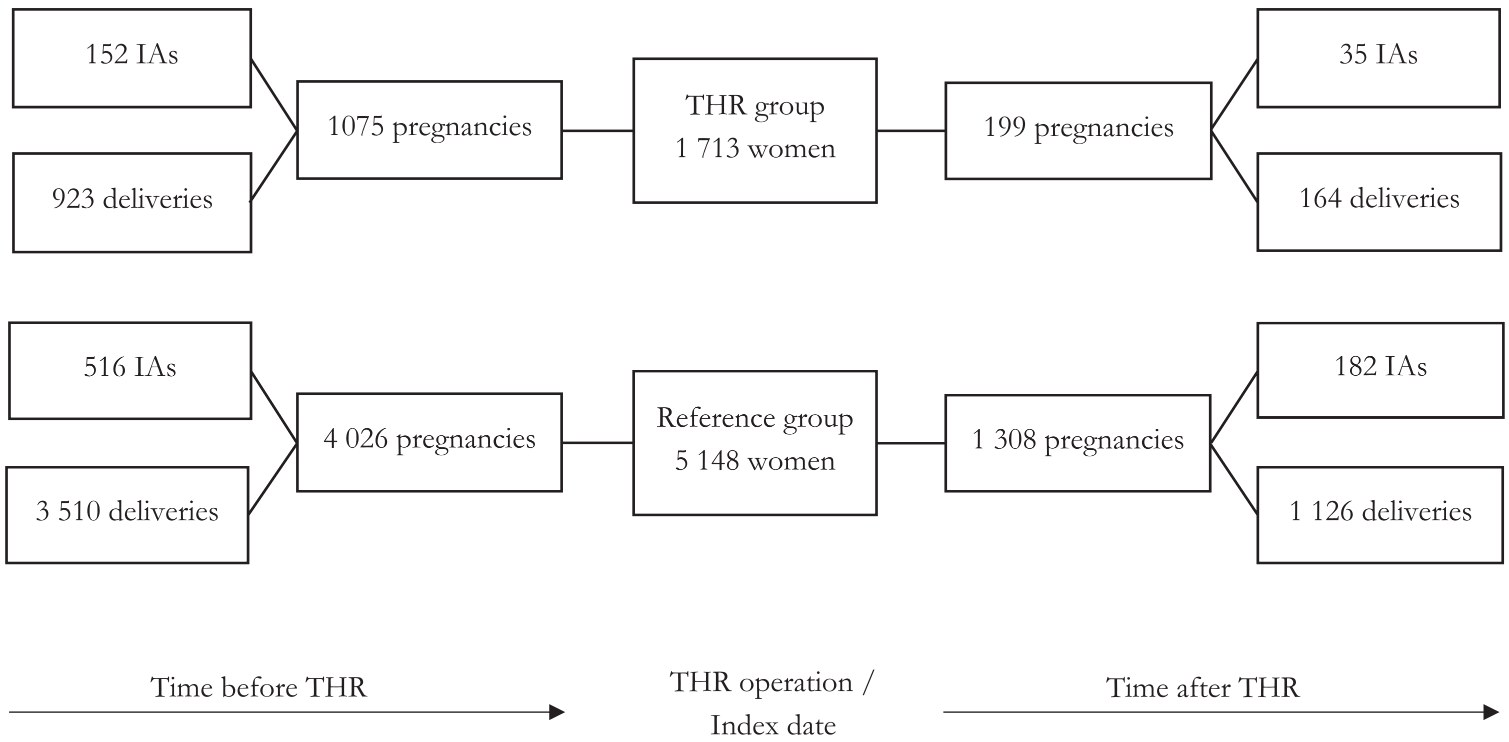
4.3.1 Study I

In the study on birth rate after THR (I), all women aged between 15 and 45 at the time of THR and all men aged 15 to 49 at the time of the THR operated between 1980 and 2007 were included in the study and formed the THR group. The THR group comprised 2 429 women and 3 434 men. The reference group had 7 276 women and 10 299 men. Information on biological live born neonates was gathered from the PIS. Additional information obtained from the PIS included marital status, number of previous children, and date of emigration or death. Information on chronic diseases was gathered from the RMR, and the diseases selected as part of this study were RA and DM type 1, since they are both known to have a negative effect on birth rate.

4.3.2 Study II

In the study on IA's after THR (II), all women aged between 15 and 44 years at the time of their first primary THR performed between 1987 and 2007 were included. If the first operation during this period was a revision, the person was excluded. Information on these operations was obtained from the FAR. Of the 2 429 THR patients identified, 1 713 were included and formed the THR group in this study. For every patient in the THR group, three reference persons were obtained and only the matching referents (5 148) were included and formed the reference group. Information on induced abortions was gathered from the RIA for the period 1987 to 2007. Further, information on pregnancies was obtained for the same period from the MBR for both the THR and reference group. Information on chronic diseases was obtained from the RMR. In this study, RA was the only disease selected for analysis. The study population and events are shown in figure 5.

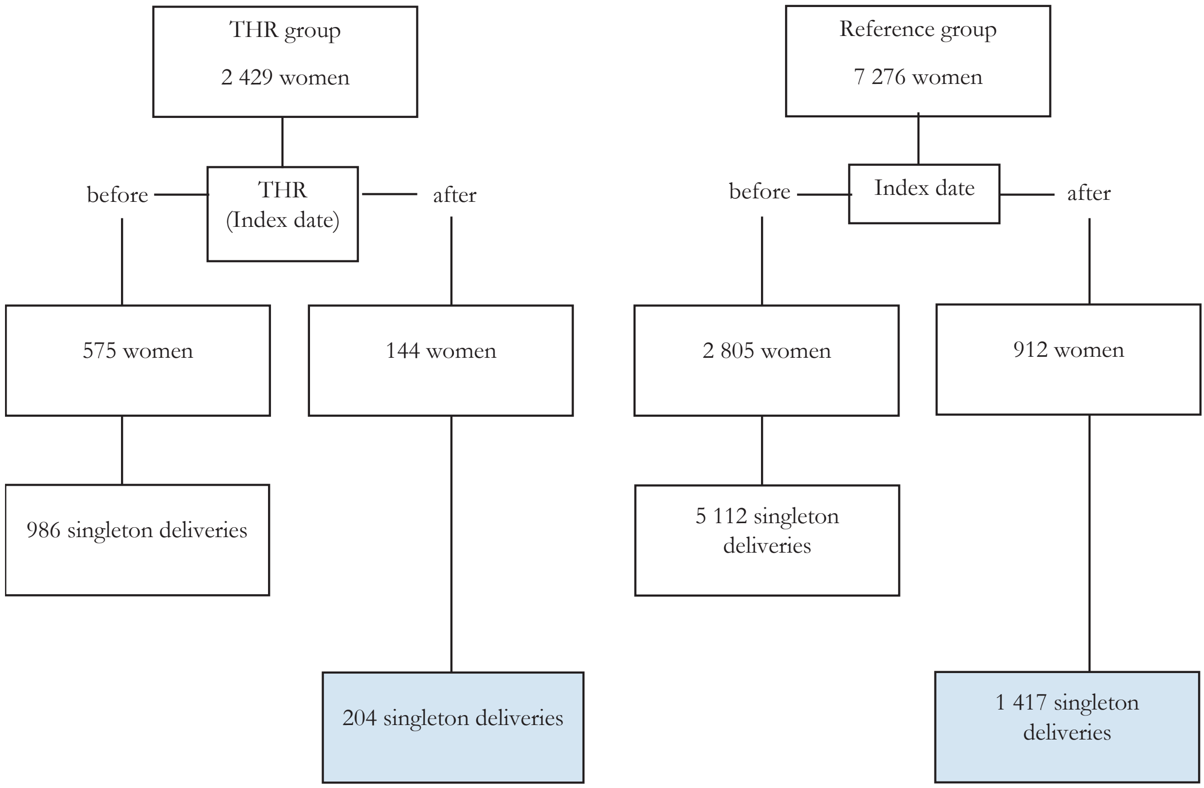
Figure 5. Flow chart of study population and events in the second part of the study, where risk for pregnancy ending in Induced abortion after THR was studied. Women aged 15 to 44 years old at the time of operation were included and three matching referents without THR were selected.
IA= Induced Abortion, THR=total hip replacement



4.3.3 Study III

In the study on delivery outcome and method after THR (III), all the women aged 15 to 45 who had undergone a THR operation between 1980 and 2007 were selected from the FAR and formed the THR group. Their matching referents without THR formed the reference group. Information on pregnancies was obtained from the MBR from 1987 to 2007. All singleton pregnancies ending in delivery were included in the study. Twin and other multiple pregnancies were excluded. Deliveries were included both before and after the THR / index date in the referents. A total of 2 429 women formed the THR group, and 7 276 women were in the reference group. (Figure 6) For the THR group, information on THR bearings was classified as MoM or non-MoM. Information on chronic diseases were obtained from the RMR and RA was the only chronic disease to be part of the analysis, since the prevalence of all the other chronic diseases remained under 1%.

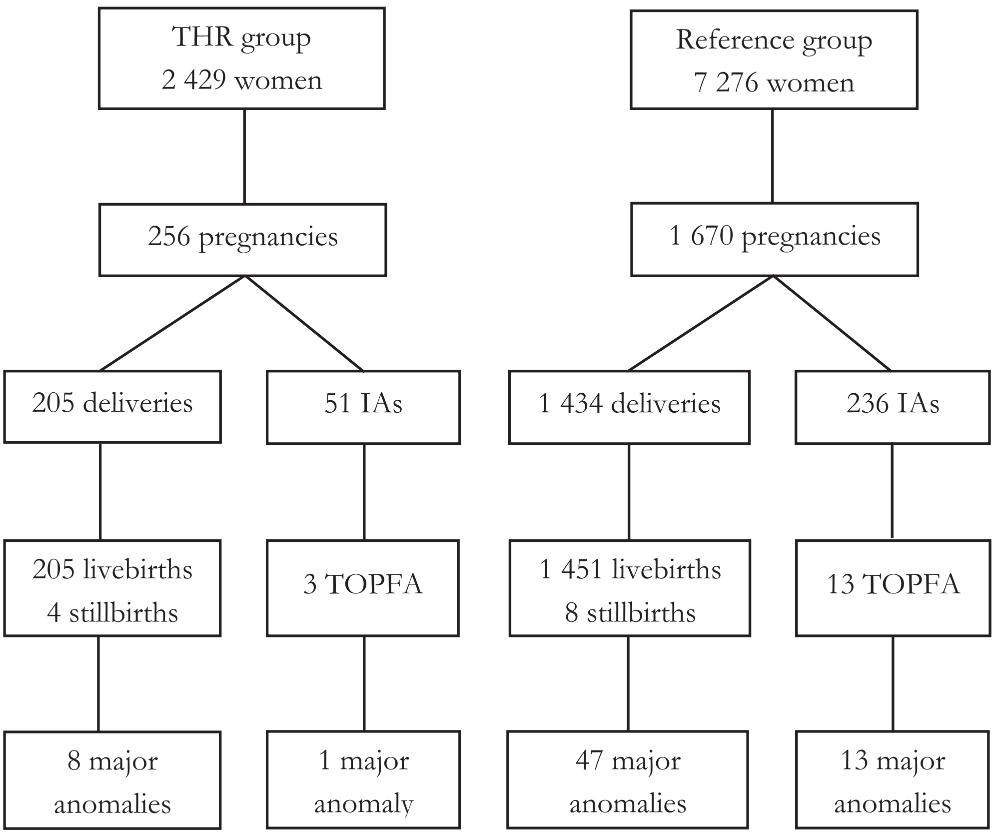
Figure 6. Flow chart of the study population and deliveries in the patient group (women with total hip replacement (THR)) and the control group. Index date is the date of THR. Deliveries of the patient group were classified as taking place before or after THR, and likewise the deliveries of the control group were matched according to the index date.



4.3.4 Study IV

In the study on congenital anomalies after THR (IV), all women aged 15 to 45 at the time of THR who were operated between 1980 to 2007 were included and formed the THR group. The matching referents without THR formed the reference group. Information on pregnancies was obtained from the MBR, RIA, and RCM for the period 1987 to 2007. (Figure 7) Information on THR bearings was gathered for the THR group and classified as MoM or non-MoM.

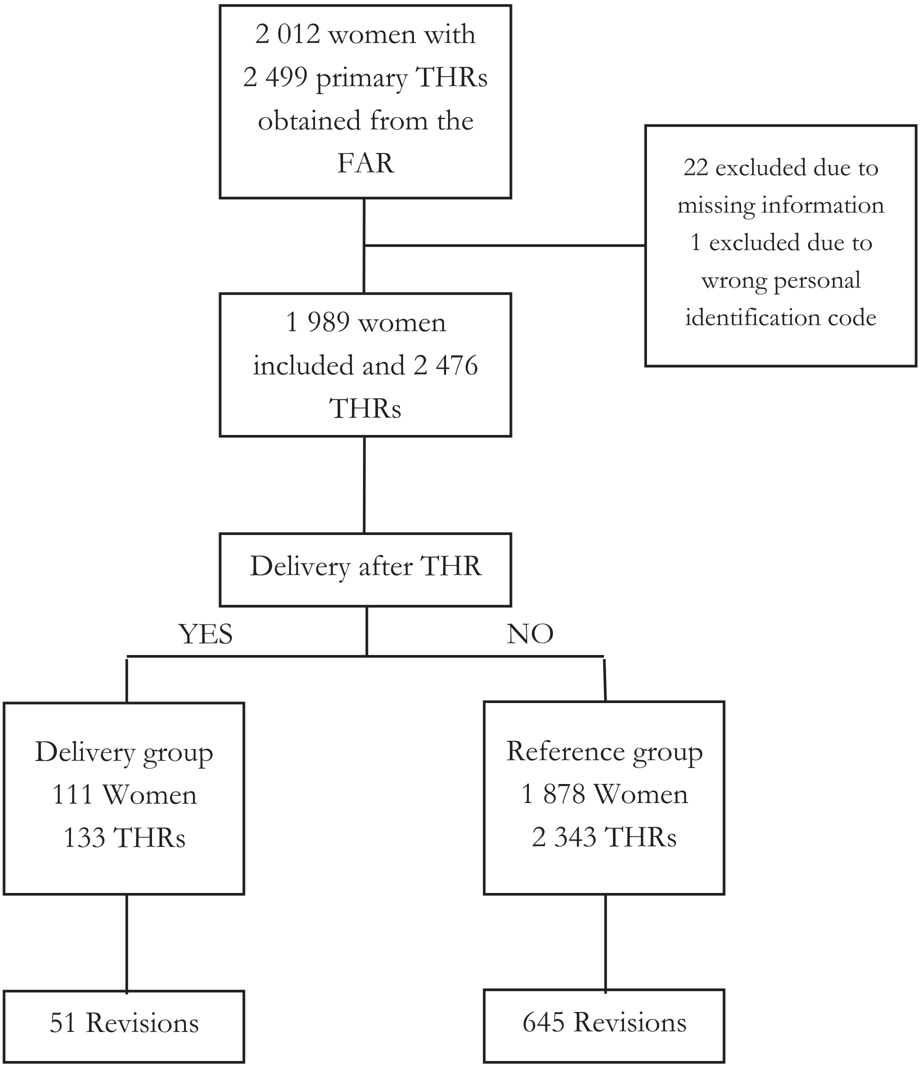
Figure 7. Flow chart of study population and events in the study on congenital anomalies after THR (IV)
IA= Induced abortion, THR= total hip replacement, TOPFA= termination of pregnancy due suspected fetal anomaly



4.3.5 Study V

For this part of the study of the 2 429 women who underwent THR between 1980 and 2007, only their primary THRs operated from 1987 to 2007 were included. In total, 2012 women with 2 499 THRs matched the criteria. Of these, 23 were excluded due to important missing information. During the study period, 111 women with 133 THRs had at least one delivery after primary THR and during the follow-up and formed the delivery group. In addition, 1 878 women with 2 343 THRs had no deliveries after THR and formed the reference group. The start of the THR survival follow-up was the operation day of the primary THR. If the woman had both hips operated during the study period, both THRs were followed independently. The endpoint for the follow-up was either the first revision of the hip, date of death, or the common end date of the study (31.12.2007), whichever came first. (Figure 8) Information on RA diagnosis was obtained from the RMR.

Figure 8. Flow chart of study population and events in the study on primary THR survival after delivery
FAR= Finnish arthroplasty register, THR = total hip replacement



4.4 Statistical Methods

4.4.1 Statistics overall

Statistical analyses were performed mainly by SPSS for Windows statistical analysis software versions 18.0-25.0. STATA v.8.2 was used for the first study and a P-value under 0.05 was considered statistically significant in all analyses.

Basic statistical key numbers were calculated. For continuous variables, in Gaussian population means with standard deviations were calculated and in non-Gaussian population medians with interquartile ranges were used. Students two-way t-test was used to evaluate the statistical differences of normally distributed continuous variables, and Mann-Whitney U-test was used for non-normally distributed variables.

For categorized variables, proportions were counted and, if needed, 95% CI. Chi square test or Fischer's exact test was used to analyze the statistical differences of the categorized variables between patient group and reference group. The test was not eligible if intergroup differences inside the patient group or reference group were analyzed before the start of the follow-up and during the follow-up, since the same woman could appear in both groups and possibly multiple times. Instead, we used the 95% CI for the proportional difference between two proportions. The difference was statistically significant if the 95% CI range was positive.

Generally, the start of the follow-up was the day that the person underwent THR. The same date was used as the index date for the three matching individuals in the reference group without THR.

4.4.2 Birth rate after THR (study I)

The start of the follow-up was the THR operation day and the same day was used for the matching referents. The endpoint for the follow-up was the date of the first live-born child or the date of emigration or date of death, or the common closing date of this study (26th of January 2011), whichever occurred first.

The Cox proportional regression model was used to evaluate risk and calculate HR for the first liveborn child after THR in relation to the reference group without

THR. Stratified analyses were conducted by age at the start of the follow-up (< 20, 20–34, 35–39 and ≥ 40 years) number of live births before THR / index date, marital status, DM, and RA. Separate adjusted Cox multivariable analyses with the following potential modifiers were conducted: age at the time of THR (continuous), marital status, previous children, DM, and RA. All the analyses were performed separately for men and women.

4.4.3 Induced abortions (II)

In the second part of the study, logistic regression model was used to count adjusted odds ratios (ORs) with 95% CI for pregnancy ending in IA after THR and before THR compared with the reference group without THR. Variables taken as part of the adjusted models and that were potential modifiers were previous deliveries, previous IAs, age at the time of IA, and marital status. IA indications, and rates were compared between the groups both before and after THR / index date. IA rates were counted per 1 000 person years and per 100 births for both groups. The start of the IA follow-up was either the 1st of January 1987 or the 15th birthday of the woman, whichever came first. The end of the IA follow-up was either the 45th birthday, date of death, date of immigration, or the 31st of December 2007, whichever occurred first. IA follow-up periods are referred to as before the THR / index date and after THR / index date. In this study, the intergroup comparison between before and after THR / index date was done by the 95% CI of the PD of the variable.

4.4.4 Pregnancies, deliveries and neonates after THR (III)

Pregnancies were observed and compared between the THR group and the reference group both before and after THR / index date. Diagnoses of small for gestational age (SGA) and large for gestational age (LGA) were calculated separately for boys and girls according to the standards of the new Finnish growth references (Saari et al., 2011). An SD lower than -2.0 was classified as SGA and an SD higher than +2.0 was classified LGA. A neonate weighing under 2 500 grams was classified as LBW. Neonates born before gestational week 37+0 were classified as preterm. The neonatal death rate comprised stillbirths and neonates who died before the age of 8 days postpartum. Logistic regression model was used to calculate adjusted ORs for adverse pregnancy and neonatal outcomes (Stillbirth, SGA, LBW and Preterm). Adjustments were made using the following covariates: maternal age at delivery, smoking during pregnancy, and maternal RA.

4.4.5 Congenital anomalies in the offspring of THR patients (IV)

Congenital anomalies after THR were analyzed in the fourth part of the study. ORs with 95% CI for major congenital anomaly in the patient group in comparison to the reference group were calculated. Subgroup analysis was performed in which the MoM implant's risk for congenital anomalies in the offspring was compared with the non-MoM THR. For both groups' anomaly types were also categorized by the ICD-10 classification and compared between groups.

4.4.6 Survival of the THR after delivery (V)

In the final part of the study, Kaplan-Meier analysis with 95% CI was performed to evaluate the survival of the hip after delivery compared with women without deliveries. Kaplan Meier survival rates were counted until there were 20 at risk in the model. The start of the follow-up was the day of the primary operation of the hip. Since the presumptions of the Cox proportional model were not met due to the crossing of the survival curves in the Kaplan Meier analysis, the piecewise Cox proportional hazard model was performed to evaluate the possible confounders and count HR for risk of revision in any indication after delivery in relation to the reference group without deliveries. Adjustments taken as part of the piecewise Cox model were age at the time of THR, RA, stem fixation, and cup fixation. Intervals before and after the crossing of the curves were analyzed independently. Bilateral observations were included, since previous studies have shown that this does not bias the results (Lie, Engesaeter, Havelin, Gjessing, & Vollset, 2004; Ranstam & Robertsson, 2010).

4.5 Ethics and permissions

4.5.1 Ethics of the study

In accordance with the instructions of the local Ethical Committee of Pirkanmaa Hospital District our register-based cohort study did not need ethical approval, and therefore it did not undergo ethical evaluation by the local ethical committee (TAYS, 2017). However, this study has been conducted according to the standards and good scientific practice set by the World Medical Association's Declaration of Helsinki.

4.5.2 Research permission

For the purposes of scientific research, data could be processed and no written consent from the data subjects were required because, in accordance with Section 14.1 of the Personal Data Act (523/1999) and the New European GDPR, research could not have been carried out without data identifying the person and the consent of data subjects could not have been obtained due to the quantity of the data and the number of subjects. Permission for the processing of the data was granted by the data controllers after evaluating our research plans and applications. Permission number: THL/599/5.05.00/2010.

5 SUMMARY OF THE RESULTS

5.1 Birth and pregnancy rate after THR (Study I, II, III, IV)

In study I, the THR patient group comprised 3 434 men and 2 429 women, and the reference group comprised 10 299 men and 7 276 women. The mean follow-up time was 11 (0-31) years for patients and 11 (0-31) years for referents among men, and 14 (0-31) years for patients and 14 (0-31) years for referents among women. The mean age at the start of the follow-up was 43 years (15-50) among men and 38 years (15-46) among women. During the follow-up, the number of first liveborn children after THR was 435 among the patients and 2 213 among the referents (Table 6). The overall birth rate in Study I was 0.07 children per male for male THR patients and 0.11 children per male for male referents. The livebirth rate for female THR patients in this study was 0.07 per female and 0.15 per female for female referents. In study I, only the first birth after THR was included.

In the studies II, III, and IV, the pregnancy and birth rates were lower in patients with THR compared with reference women without THR. When the IAs were included, the pregnancy rate for the THR patients included in study II was 0.12 pregnancies per woman after THR. In the reference group, the rate was 0.25 pregnancies per woman. The overall pregnancy rate in study II was 0.96 per woman during the study period 1987 to 2007. The results of study II are presented in more detail later. The IAs were also included in study IV in which all the patients were included. In study IV, the pregnancy rate after THR was 0.11 per woman in the THR patient group and 0.23 per woman in the reference group.

In the third part of the study, all singleton deliveries were analyzed after THR instead of only the first delivery analyzed in study I. The mean number of children after THR was 0.08 in the THR patient group during the follow-up. In the reference group, the mean number of children after index date was 0.19. The birth rate in study IV was 0.08 livebirths (multiple births included) per woman in the THR patient group after THR and 0.20 livebirths per woman in the reference group after index date.

Table 6. Number of subjects and livebirths in patients with total hip arthroplasty (THA) and referents without THA according to age at start of follow-up, number of previous liveborn children before THA, marital status, Diabetes Mellitus diagnosis, and Rheumatoid Arthritis diagnosis, Finland 1985-2006

	Men				Women			
	No. of subjects		No. of livebirths		No. of subjects		No. of livebirths	
	patient	referent	patient	referent	patient	referent	patient	referent
Total	3 434	10 299	254	1 104	2 429	7 276	181	1 109
Age at the start of the follow-up								
15-19	28	84	6	29	50	150	15	90
20-34	414	1 240	127	571	621	1 847	140	824
35-39	509	1 528	64	257	571	1 722	22	167
40-45	1 151	3 465	36	193	1 187	3 557	4	28
46-50	1 332	3 982	20	54	N/A	N/A	N/A	N/A
No. of previous liveborn children								
0	1 101	2 984	95	435	831	1 871	100	552
1 or more	2 333	7 315	159	669	1 598	5 405	81	557
Marital status								
never married	887	2 466	32	183	628	1 370	34	190
ever married	2 547	7 833	222	921	1 801	5 906	147	919
Diabetes Mellitus								
yes	87	174	4	6	35	48	2	4
no	3 347	10 125	250	1 098	2 394	7 228	179	1 105
Rheumatoid arthritis								
yes	505	86	44	4	811	68	70	6
no	2 929	10 213	210	1 100	1618	7 208	111	1 103

The birthrate varied by age at the start of follow-up, number of previous liveborn children before THR, and marital status (Table 7). However, the birthrate was lower in all patient groups when compared with referents among both genders regardless of number of previous children. Male patients with THR and DM had a higher birthrate than their referents without THR but with DM. The same was seen among male patients with THR and RA. In women, the birthrate was lower in patients with either DM or RA and THR than among referents. The birthrate was also lower in all age groups of the patient population compared with referents. These differences were especially obvious among women in the 2 youngest age groups and among male patients aged between 20 and 35 years.

Table 7. Birthrate (per 10 000 person-years) with 95% confidence interval (CI) in patients with total hip replacement (THR) and referents without THR according to age at start of follow-up, number of previous liveborn children before THR, marital status, Diabetes Mellitus diagnosis, and Rheumatoid Arthritis diagnosis, Finland 1985-2006.

	Men				Women			
	Patient		Referent		Patient		Referent	
	Rate	95% CI	Rate	95% CI	Rate	95% CI	Rate	95% CI
Total	67	59 – 75	95	89 - 100	52	45 - 60	110	104 – 116
Age at the start of the follow-up								
15-19	216	97 – 480	377	262 – 542	216	130 – 358	570	463 – 700
20-34	300	252 – 357	515	474 – 559	165	140 – 195	400	374 - 429
35-39	114	89 – 145	149	132 – 169	25	16 – 38	63	54 – 74
40-45	27	20 – 38	47	41 – 54	2.4	0.9 – 6.4	5.4	3.7 – 7.8
46-50	13	8.7 – 21	12	8.9 – 15	N/A	N/A	N/A	N/A
No. of previous liveborn children								
0	82	67 – 100	145	132 – 159	86	70 – 104	247	227 – 268
1 or more	60	51 – 70	77	72 – 83	35	28 – 44	71	65 – 77
Marital status								
never married	36	25 – 50	78	67 – 90	39	28 – 55	116	101 – 134
ever married	76	67 – 87	99	93 – 106	57	48 – 66	109	102 – 116
Diabetes Mellitus								
Yes	52	19 – 138	38	17 – 84	46	12 – 185	70	26 – 186
No	67	59 – 76	95	90 – 101	52	45 – 61	110	108 – 117
Rheumatoid arthritis								
Yes	64	47 – 86	40	15 – 108	53	42 – 68	73	33 – 163
no	67	59 – 77	95	90 - 101	52	43 – 62	110	104 – 117

The decreased probability of a liveborn child when patients were compared with referents could also be seen in Cox regression models (Table 3). Overall, the probability of having a liveborn child after THR was lower among males (HR 0.69, 95% CI 0.60 to 0.79) and females with THR (HR 0.47, CI 0.40 to 0.55) than referents also in adjusted analyses (men adjusted HR (aHR) 0.80, CI 0.69 to 0.92, women aHR 0.56, CI 0.46 to 0.68) (Table 8). Female patients with THR had a lower probability of having a liveborn child than their referents in all but the oldest age group (40-45 years). The same phenomenon was seen among male patients in all but the youngest age group (15-19 years). Adjustment for potential confounding factors (age at the start of the follow-up, number of liveborn children before THR, marital status, DM, and RA) lowered the probability of having a liveborn child among patients with THR compared with the referents. Among THR patients with DM or RA, however, HRs were similar.

Table 8. Table 3. Hazard ratio (HR) with 95% confidence intervals (CI) for the first liveborn child after total hip replacement (THR) among patients with THR in relation to referents without THR according to various demographic factors, Diabetes Mellitus diagnosis, and Rheumatoid Arthritis diagnosis, Finland 1985-2006.

	Men	Women
	HR (95% CI)	HR (95% CI)
Crude	0.69 (0.60–0.79)	0.47 (0.40–0.55)
Adjusted*	0.80 (0.69–0.92)	0.56 (0.46–0.68)
Age at the start of the follow-up		
15-19	0.57 (0.24–1.4)	0.34 (0.20–0.60)
20-34	0.61 (0.50–0.74)	0.43 (0.36–0.51)
35-39	0.74 (0.56–0.97)	0.38 (0.25–0.60)
40-45	0.57 (0.40–0.81)	0.43 (0.15–1.2)
46-50	1.12 (0.67–1.9)	N/A
No. of previous liveborn children		
0	0.58 (0.46–0.72)	0.36 (0.29–0.44)
1 or more	0.75 (0.63–0.89)	0.48 (0.38–0.61)
Marital status		
never married	0.48 (0.33–0.70)	0.36 (0.25–0.51)
ever married	0.74 (0.64–0.86)	0.51 (0.43–0.61)
Diabetes Mellitus		
Yes	1.32 (0.37–4.7)	0.64 (0.12–3.5)
No	0.69 (0.60–0.79)	0.47 (0.40–0.55)
Rheumatoid arthritis		
Yes	1.81 (0.65–5.1)	0.84 (0.37–1.9)
No	0.67 (0.58–0.78)	0.44 (0.36–0.54)

HR: hazard ratio. Reference (HR = 1.0) are individuals without THR.
*Hazard ratio adjusted for age at the start of follow-up, number of previous live births before THR, marital status, diabetes mellitus, and rheumatoid arthritis.

5.2 Induced abortions (II)

The THR patient group comprised 1 713 women, with 1 274 pregnancies and 187 (14.7%) IAs. Of these, 199 pregnancies and 35 (17.9%) IAs occurred after THR. The reference group comprised 5 148 women with 5 334 pregnancies and 698 (13.1%) IAs. Of these, 1 308 pregnancies and 182 (13.9%) IAs occurred after the index date. Mean age at the beginning of the abortion follow-up was 27.4 years and mean age at the THR/index date was 37.3 years in both groups. The basic demographics of both the THR patient and reference groups are presented in Table 9.

Before the THR/index date, there were 152 (14.1%) IAs in the THR patient group and 516 (12.8%) in the reference group, p=0.25. After the THR/index date, the THR patient group had 35 (17.9%) IAs and the reference group 182 (13.9%), p=0.17. In the THR patient group, the proportion of IAs increased from 152 (14.1%) before THR to 35 (17.9%) after THR (PD= 3.5, CI -1.7 - 9.7). In the reference group, the number of IAs before the index date was 516 (12.8%) and 182 (13.9%), PD= 1.1, CI -1.0 - 3.3) after the index date. The median time from THR to IA was 4.0 years (range 0.1 to 20.4 years) in the THR patient group. Before the THR, the median time from IA to THR was 8.4 years (0.2 to 20.5). Median times in the reference group were 3.9 years (0.0 to 19.7 years) after the index date, and 7.1 years (0.0 to 20.7 years) before the index date.

In the THR patient group, the abortion rate was 9.0/1 000 person years before the THR and 3.9 /1 000 person years after the THR. In the reference group, the rates were 10.2 /1 000 person years before the index date and 6.6 /1 000 person years after the index date. In the patient group, abortion rates were 17/100 livebirths before the index date and 21/100 livebirths after the index date. In the reference group, the abortion rate was 15/100 livebirths before the index date and 16/100 livebirths after the index date.

Induced abortion indications varied slightly between the women with and without THR (Table 10). More abortions were carried out for maternal health reasons in the THR patient group. The rate of the first abortion was higher after THR compared with rates before the THR and the reference group. Interestingly, married women seemed to have fewer abortions after THR than unmarried women.

Table 9. Background characteristics of study population (study II)

	THR patient group		Reference group	
	n=1713	%	n=5148	%
Age at the start* of the abortion follow-up				
15-19	340	19.8	1017	19.8
20-24	353	20.6	1062	20.6
25-29	335	19.6	1009	19.5
30-34	361	21.1	1072	20.8
35-39	230	13.4	703	13.7
40-44	94	5.5	285	5.5
Age at THR/index date				
15-19	39	2.3	117	2.3
20-24	80	4.7	236	4.6
25-29	155	9.0	465	9.0
30-34	230	13.4	684	13.3
35-39	435	25.4	1310	25.4
40-44	774	45.2	2336	45.4
Marital status				
ever married	1238	72.3	4059	21.2
never married	475	27.7	1089	78.8
Nulliparous at the start of the abortion follow-up	979	57.2	2706	52.6
Follow-up time (years + SD)				
before THR/index date	9.8	5.9	9.8	5.9
after THR/index date	5.2	4.5	5.3	4.6
Chronic diseases				
Rheumatoid Arthritis	521	30.4	42	0.8
Diabetes Mellitus	28	1.6	33	0.6
Epilepsy	6	0.4	12	0.2
Major mental disease	3	0.2	8	0.2

THR= Total hip replacement
Index date= Date of the operation in the THR patient group and the same date for matching referents.
Start of the abortion follow-up= Day of the 15th birthday or the 1st of January 1987, which ever came first.

Table 10. Total number of abortions for women with and without total hip replacement (THR) before and after THR/index date in Finland between 1987 and 2007.

	THR patient group				Reference group			
	Before THR		After THR		Before index date		After index date	
	n=152	%	n=35	%	n=516	%	n=182	%
No previous pregnancies	46	31.1	9	25.7	176	34.3	37	20.4
Previous pregnancies	102	68.9	26	74.3	337	65.7	144	79.6
No previous IA	95	63.8	28	80.0	340	66.3	115	63.5
One or more previous IA	54	36.2	7	20.0	173	33.7	66	36.5
Nulliparous	57	38.0	12	34.3	229	44.4	49	26.9
Previous delivery	93	62.0	23	65.7	287	55.6	133	73.1
Induced abortion indications								
Social reasons	118	77.6	24	68.6	447	86.6	126	69.2
Age (<18 or >40)	5	3.3	4	11.4	31	6.0	23	12.6
Maternal health	17	11.2	5	14.3	14	2.7	5	2.7
Fetal health	6	3.9	1	2.9	13	2.5	12	6.6
4+ previous births	6	3.9	1	2.9	11	2.1	16	8.8
Socioeconomic status	37	24.3	18	51.4	141	31.2	95	52.2
Upper white collar	1	2.7	3	16.7	14	8.7	20	21.1
Lower white collar	19	51.4	6	33.3	57	35.4	38	40.0
Blue collar	6	16.2	5	27.8	34	21.1	16	16.8
Other**	11	29.7	4	22.2	36	22.4	21	22.1
Age at THR/index date								
under 20	0	0.0	4	11.4	3	0.6	15	8.2
20-24	4	2.6	4	11.4	35	6.8	27	14.8
25-29	16	10.5	3	8.6	58	11.2	45	24.7
30-34	30	19.7	12	34.3	100	19.4	37	20.3
35-39	35	23.0	9	25.7	117	22.7	43	23.6
40 or more	67	44.1	3	8.6	203	39.3	15	8.2
Age at the time of abortion								
under 20	12	7.9	1	2.9	49	9.5	5	2.7
20-24	29	19.1	4	11.4	105	20.3	13	7.1
25-29	40	26.3	4	11.4	119	23.1	30	16.5
30-34	37	24.3	5	14.3	136	26.4	40	22.0
35-39	29	19.1	13	37.1	79	15.3	58	31.9
40 or more	5	3.3	8	22.9	28	5.4	36	19.8
Never married	51	33.6	12	34.3	159	30.8	46	25.3
Ever married	101	66.4	23	65.7	357	69.2	136	74.7
No RA	131	86.2	24	68.6	509	98.6	182	100.0
RA	21	13.8	11	31.4	7	1.4	0	0.0

Women in the THR patient group were more likely to undergo their first IA after THR rather than before THR or women in the reference group. Women in the youngest and the oldest age groups had higher IA proportions than those in the moderate age groups. Women with previous IA had higher rates of pregnancies ending in IA in both the THR patient and reference groups. Ever married women had significantly lower IA proportions than those never married in both groups. RA patients had no differences in IA proportions. Table 12

Unadjusted OR for pregnancy ending in induced abortion in the THR patient group after THR/index date was 1.32 (CI 0.89 – 1.96), p=0.17, in relation to the reference group (Table 11). When adjusted with the variables of marital status, age (<20 or >39), previous IAs, and previous deliveries, there was a trend for higher risk for pregnancy to end in IA in the THR group in relation to the reference group (OR was 1.50, CI 0.99 – 2.28; p=0.05). In this logistic model, age, marital status and previous IA significantly increased the risk for pregnancy ending in IA.

Table 11. Odds ratios (OR)s with 95% Confidence intervals (CI) for pregnancy ending in induced abortion of women with total hip replacement (THR) in relation to the reference cohort of women without THR before and after THR/index date, Finland 1987-2007.

	Before THR/index date			After THR/index date		
	Univariate OR	95% CI	p-value	Univariate OR	95 %CI	p-value
THR patient group	1.12	0.92-1.36	0.25	1.32	0.89-1.96	0.17
Age	5.51	4.16-7.29	<0.001	2.42	1.69-3.47	<0.001
Never married	3.50	2.91-4.23	<0.001	1.89	1.35-2.64	<0.001
Previous delivery	0.80	0.68-0.95	0.008	1.26	0.92-1.73	0.15
Previous IA	5.79	4.76-7.04	<0.001	4.49	3.20-6.28	<0.001
Adjusted OR for patient group	1.09	0.88-1.34	0.46	1.50	0.99-2.28	0.05

Table 12. Proportions of pregnancies ending in induced abortion with 95 % Confidence intervals (CI) among women with and without total hip replacement (THR) before and after THR/index date in Finland between 1987 and 2007.

	THR patient group				Reference group			
	Before THR		After THR		Before index date		After index date	
	%	CI	%	CI	%	CI	%	CI
Previous pregnancies								
0	14.7	10.8 – 18.6	17.0	8.7 – 25.3	15.3	13.2 – 17.3	12.3	8.3 – 16.2
1+	13.5	11.1 – 15.9	17.8	11.8 – 23.8	11.8	10.7 – 13.0	14.4	12.0 – 16.7
Previous abortions								
0	11.0	8.9 – 13.1	16.2	10.8 – 21.6	10.2	9.1 – 11.2	10.7	8.7 – 12.6
1+	41.5	33.1 – 50.0	36.8	23.1 – 50.6	39.6	35.0 – 44.2	36.7	27.8 – 45.5
Previous births								
0	13.5	10.2 – 16.8	16.2	8.9 – 23.6	15.1	13.3 – 16.9	11.9	8.6 – 15.2
1+	14.4	11.7 – 17.1	18.4	11.9 – 24.9	11.6	10.3 – 12.8	14.9	12.4 – 17.4
Age at the time of abortion								
15-29	46.2	27.0 – 65.3	100.0	0.0 – 100.0	55.1	44.7 – 65.4	50.0	6.2 – 93.8
20-24	20.1	13.6 – 26.7	28.6	15.4 – 41.8	19.8	16.4 – 23.2	18.1	8.2 – 27.9
25-29	10.6	7.5 – 13.8	11.4	3.8 – 19.1	8.5	7.0 – 10.0	11.0	7.1 – 27.9
30-34	10.1	7.0 – 13.2	8.1	2.5 – 13.6	10.0	8.4 – 11.6	9.2	6.3 – 12.0
35-39	19.9	13.4 – 26.3	22.4	13.3 – 31.6	14.2	11.3 – 17.1	15.9	11.8 – 20.0
40-44	31.3	8.5 – 54.0	27.6	15.9 – 39.3	30.8	21.3 – 40.3	23.7	15.9 – 31.4
Marital status								
Never married	31.5	24.5 – 38.9	38.7	25.7 – 51.7	28.3	24.6 – 32.0	19.5	13.9 – 25.1
Ever married	11.1	9.0 – 13.1	13.7	8.7 – 18.7	10.3	9.3 – 11.3	12.7	10.6 -14.8
Rheumatoid arthritis								
No	15.0	12.6 – 17.4	20.3	13.4 – 27.3	12.8	11.7 – 13.8	14.0	12.0 – 16.0
Yes	10.4	6.2 – 14.7	13.6	7.0 – 20.1	17.1	5.6 – 28.6	0.0	0.0 – 0.0

5.3 Deliveries (III)

The THR group comprised 2 429 women, 719 (29.6%) of whom had 1 190 pregnancies ending in singleton deliveries. Prior to THR, 575 women had 986 singleton deliveries, and 144 women had 204 singleton deliveries after THR. The reference group comprised 7 276 women, 2 805 (38.6%) of whom had 5 112 pregnancies ending in singleton deliveries. Of those, a total of 1 893 women had 3 695 singleton deliveries before the index date, and 912 women had 1 417 singleton deliveries after the index date. The mean age at birth after THR/index date in the THR group was 33.4 years and 32.6 years in the reference group, p=0.046. Smoking habits during pregnancy and marital status did not differ between groups. Women in the THR group had a naturally higher rate of RA than those in the reference group without THR. Baseline information and background characteristics of the pregnant women are described in Table 13.

The proportion of elective CS was higher after THR in the THR group than in the reference group after the index date. The CS rate was, however, also slightly higher in the THR group before THR than in the reference group before the index date. Trial of labor resulted significantly more often in acute CS in the THR group after THR. Women in the THR group also had a higher rate if they had a previous CS. Women spent more time in hospital both before and after delivery in the THR group compared with women in the reference group. (Table 13).

Comparisons of labor analgesia and delivery related procedures in attempted vaginal deliveries are shown for both the THR and the reference group before and after THR/index date in Table 14. There was no difference in the proportions of vacuum and forceps extractions between the groups. The use of epidural analgesia was more common in the reference group after THR/index date. Use of non-pharmaceutical analgesia was similar between the groups. Episiotomy was more common in the reference group after index date. Amniotomy was performed more often in the reference group than in the THR group after THR/index date. The third stage of labor was equally successful in all the groups. (Table 14)

Table 13. Background characteristics of mothers having singleton pregnancies ending in delivery before and after THR / index date. Index date is the date the matching women underwent THR in the THR group.

	Before THR/index date					After THR/ index date				
	THR group		Reference group			THR group		Reference group		
	n=986	% or SD	n=3695	%	p	n=204	%	n=1417	%	p
Age at birth -mean (SD)	29.6	4.7	29.9	4.7	0.12	33.4	5.2	32.6	5.2	0.046
Nulliparous	385	39.0	1331	36.0	0.08	80	39.2	438	31.0	0.02
Previous cesarean section	90	9.1	244	6.6	0.006	37	18.1	161	11.4	0.006
Marital status										
never married	112	11.4	428	11.6	0.85	28	13.7	205	14.5	0.78
ever married	874	88.6	3267	88.6		176	86.3	1212	85.5	
Maternal smoking										
non-smoker	796	80.7	3069	83.1	0.13	173	84.1	1191	84.1	0.63
quit during 1st trimester	41	4.2	125	3.4		4	2.0	43	3.0	
Smoker	122	12.4	380	10.3		25	12.3	142	10.0	
Mothers baseline disease										
Rheumatoid arthritis	187	19.0	42	1.1	<0.001	86	42.2	6	0.4	<0.001
Days in hospital (mother)										
total (median+interquartiles)	5	4/6	4	3/6	<0.001	5	4/6	4	3/6	<0.001
after birth	3	2/5	3	2/4	0.002	3	2/5	3	2/4	<0.001
Intended mode of delivery										
elective CS	127	12.9	259	7.5	<0.001	69	33.8	124	8.8	<0.001
trial of labor	859	87.1	3436	92.5		135	66.2	1293	91.2	
Actual mode of delivery in TOL										
spontaneous vaginal	677	79.2	2893	84.5	<0.001	93	68.9	1056	82.1	<0.001
vacuum or forceps	35	4.1	174	5.1		3	2.2	84	6.5	
acute CS	143	16.7	358	10.4		39	28.9	150	11.6	

Table 14. Amount and proportion of use of labor analgesia and comparison of delivery related procedures performed in attempted vaginal deliveries for both the patient group and the reference group before and during follow-up. Index date is the day the patient in the THR group underwent THR, and it is used as the index date for three matching referents in the reference group.

	Before THR/ index date					After THR/ index date				
	THR group		reference group			THR group		reference group		
Total number	859		3436			135		1293		
	n	%	n	%	P	n	%	n	%	p
Mode of delivery										
spontaneous vaginal	677	79.2	2893	84.5	<0.001	93	68.9	1056	82.1	<0.001
vacuum or forceps extraction	35	4.1	174	5.1	0.23	3	2.2	84	6.5	0.05
acute caesarean section	143	16.7	358	10.4	<0.001	39	28.9	150	11.6	<0.001
Use of analgesia										
Epidural	149	17.3	582	16.9	0.78	23	17.0	334	25.8	0.03
Spinal	0	0.0	8	0.2	0.16	2	1.5	30	2.3	0.53
Paracervical	134	15.6	578	16.8	0.39	18	13.3	219	16.9	0.28
Delivery related procedures										
Amniotomy	225	26.2	1051	30.6	0.01	33	24.4	516	39.9	<0.001
oxytocin augmentation	215	25.0	886	25.8	0.65	39	28.9	467	36.1	0.10
Prostaglandins	50	5.8	144	4.2	0.04	10	7.4	88	6.8	0.79
Episiotomy	237	27.6	1009	29.4	0.31	28	20.7	372	28.8	0.05
placenta removal	9	1.0	35	1.0	0.94	1	0.7	15	1.2	0.66
uterine curettage	11	1.3	33	1.0	0.41	1	0.7	18	1.4	0.53

5.4 Neonate outcome (III)

Stillbirth was more common in the THR group after THR compared with the reference group after the index date. The rate of stillbirth was also higher after THR compared with before THR (4 (2.0%) vs 3 (0.3%), proportional difference 1.7 (95% CI: 0.3 – 4.6)), (Table 15). Perinatal mortality rates were similar between THR and reference groups. After THR, neonates had a lower birthweight and birth height and were more likely to be born preterm compared with the reference group and before THR. In addition, neonates born after THR also had higher LBW, VLBW, and SGA proportions. The proportion of LGA was lower after THR in the THR group compared with other groups. Furthermore, neonates born after THR needed more neonatal high dependency care unit treatment and phototherapy compared with the reference group and before THR. Delivery related asphyxia rates were similar in both groups before and after THR/index date. Resuscitation and respiratory treatments were rare in all groups and there were no differences in the neonatal intensive care unit admissions between the groups. Table 15

When these findings were adjusted with potential confounders (maternal age at delivery, smoking during pregnancy, and maternal rheumatoid arthritis), THR remained as an independent risk factor for preterm birth, LBW, and SGA, but not for stillbirth. The unadjusted OR for stillbirth after THR was 3.52 (95% CI 1.05 – 11.81) and the adjusted OR was 2.72 (95% CI 0.58 – 12.67). Women with THR also seemed to have a higher risk for preterm birth before THR compared with women without THR (Table 16).

Table 15. Information on singleton-born neonates before and after THR / index date in the patients with THR and the reference group without THR in Finland from 1987 to 2007

	Before THR/index date					After THR/index date				
	THR group		Reference group			THR group		Reference group		
Total number	986		3695			204		1417		
	n	%	n	%	p	n	%	n	%	p
Fetal gender male	524	53.1	1898	51.4	0.36	103	50.5	730	51.5	0.78
Height cm (SD)	50.0	2.4	50.3	2.5	0.002	48.7	2.8	50.3	2.6	<0.001
Weight (grams, SD)	3520	580	3560	560	0.03	3240	670	3580	560	<0.001
LBW <2500g	40	4.1	114	3.1	0.13	25	12.3	41	2.9	<0.001
VLBW <1500g	5	0.5	18	0.5	0.94	6	2.9	9	0.6	0.001
SGA	33	3.3	106	2.9	0.43	17	8.3	39	2.8	<0.001
LGA	38	3.9	126	3.4	0.50	3	1.5	57	4.0	0.04
Preterm, <37+0 weeks	70	7.1	170	4.6	0.002	28	13.7	65	4.6	<0.001
Perinatal mortality	6	0.6	20	0.5	0.81	4	2.0	10	0.7	0.09
Stillbirths	3	0.3	13	0.4	0.66	4	2.0	8	0.6	0.02
Neonatal deaths	3	0.3	7	0.2	0.45	0	0.0	2	0.1	0.99
1-minute Apgar score ≤ 6	33	3.4	135	3.7	0.65	13	6.4	73	5.2	0.47
Delivery related asphyxia	14	1.4	50	1.4	0.87	5	2.5	35	2.5	0.99
Antibiotic treatment	22	2.2	74	2.0	0.65	11	5.4	46	3.2	0.12
Phototherapy	47	4.8	145	3.9	0.24	19	9.3	63	4.4	0.003
Resuscitation	5	0.5	17	0.5	0.85	1	0.5	11	0.8	0.54
Respirator treatment	8	0.8	24	0.6	0.58	4	2.0	14	1.0	0.22
High-dependency care	61	6.2	211	5.7	0.57	27	13.2	112	7.9	0.01
Intensive-care unit	26	2.6	109	2.9	0.60	8	3.9	38	2.7	0.32
At home 7 days of age	825	84.6	3233	88.4	<0.001	169	82.8	1284	91.4	<0.001
In hospital 7 days of age	144	14.8	403	11.1		31	15.2	111	7.9	

Table 16. Univariable and adjusted Odds ratios (OR) with 95% confidence intervals (CI) and p-values for pregnancy outcomes in Finland from 1987 to 2007. Patient group compared with reference group before and after THR/index date. Index date is the date the matching women underwent THR in the THR group.

	Stillbirth				Preterm				SGA				LBW			
	OR	95% CI		P	OR	95% CI		p	OR	95% CI		p	OR	95% CI		p
		lower	upper			lower	upper			Lower	upper			lower	upper	
Before THR/index date																
Univariable	0.82	0.25	3.04	0.86	1.59	1.19	2.11	0.002	1.17	0.79	1.74	1.02	1.33	0.92	1.92	0.13
Adjusted*	0.98	0.28	3.46	0.98	1.53	1.13	2.08	0.007	1.02	0.66	1.57	0.94	1.19	0.80	1.78	0.39
After THR/index date																
Univariable	3.52	1.05	11.81	0.04	3.31	2.07	5.30	<0.001	3.21	1.78	5.79	<0.001	4.67	2.77	7.87	<0.001
Adjusted*	2.72	0.58	12.67	0.20	3.58	2.03	6.30	<0.001	2.83	1.35	5.93	0.006	4.79	2.56	8.97	<0.001

SGA = small for gestational age

LBW = low birth weight (under 2500 grams)

* Data were adjusted by the following variables: maternal age at delivery, smoking during pregnancy, and maternal rheumatoid arthritis.

In subgroup analysis, the MoM-implant THR group was compared with the non-MoM implant group. There were 16 pregnancies and neonates in the MoM group and 188 pregnancies in the non-MoM THR group. No stillbirths occurred in the MoM group. The groups had no differences in the rates of stillbirths, preterm births, and LBW neonates. The MoM implant group had a higher rate of SGA neonates than the non-MoM group (25.0% vs 6.9%, p=0.03). The SGA rate in the MoM implant group was also significantly higher compared with the rate in the reference group (25.0 % vs 2.8 %, p<0.001). (Table 17)

Table 17. Pregnancy outcomes after total hip replacement (THR), THR patients with metal-on-metal (MoM) implants compared with non-MoM implant THR patients by chi square test.

	MoM THR		non-MoM THR		
	n=16	%	n=188	%	p-value
Stillbirth	0	0.0	4	2.1	1.00
Preterm	4	25.0	24	12.8	0.25
SGA	4	25.0	13	6.9	0.03
LBW	3	18.8	22	11.7	0.42

SGA = Small for gestational age
LBW = low birthweight

5.5 Congenital anomalies (IV)

In the THR patient group, a total of 2 429 woman had 256 pregnancies, and 80.1% of those (n=205) ended in delivery, and the remaining 19.7% (n=51) ended in IA. In the reference group, 7 276 women had 1 670 pregnancies of which 86.4% (n=1 434) ended in delivery and 13.6% (n=236) in IA, p=0.02. The mean age at the start of the follow-up was 37.7 years (SD 0.1) in both groups.

In the THR patient group, 209 births occurred of which 205 (98.1%) were livebirths and 4 (1.9%) stillbirths, respectively. Eight (3.8%) neonates had one or more major anomaly. In the THR patient group, 3 (5.9%) of the 51 IAs were performed due to suspected fetal defects. Of these, 1 had at least one major anomaly recorded to the register. In the reference group, a total of 1 451 births occurred of which 1 443 (99.4%) were livebirths and 8 (0.6%) stillbirths. In total, 47 (3.3%) neonates had one or more major anomaly. In this group, 13 (5.5%) of the 236 IAs were performed due to suspected fetal defects, and all of them had at least one major anomaly recorded to the register. No major differences between these group were observed. The background characteristics and a comparison between the groups are presented in Table 18.

In the subgroup analysis, women who had undergone MoM THR had 19 births/fetuses with 2 (10.5%) major anomalies. There was no significant difference in the incidence of major anomalies between women with a MoM THR (10.5%, n=2/19) and those with a non-MoM THR (3.0%, n=7/241), OR being 3.93 (95% CI 0.76 – 20.2, p=0.13). Furthermore, there was no significant difference in incidence between women with a MoM THR and those without THR (3.6%, n=60/1687; p=0.15).

Table 18. Total number of births/terminated pregnancies due to fetal anomaly, number of outcomes with malformation in the THR cohort and the reference cohort, and the odds ratio (OR) with 95% confidence interval (CI) for major congenital malformation in the offspring of women with THR in relation to the reference cohort. *TOPFA = termination of pregnancy due to fetal anomaly ** Index date: the THR operation day in the THR patients was used for matched referents. *** Odds ratios counted for Metal on Metal (MoM) implant patients in relation to Non-MoM patients.

	Women with THR			Women without THR					
	Births/ fetuses	Major anomalies		Births /fetuses	Major anomalies		OR	95% CI	
	No.	No.	%	No.	No.	%		Lower	Upper
Total	260	9	3.5	1 687	60	3.6	0.98	0.48	1.98
Pregnancy outcome									
livebirth	205	8	3.9	1 443	47	3.3	1.20	0.56	2.58
stillbirth	4	0	0.0	8	0	0.0	-	-	-
Induced abortion	51	1	2.0	236	13	5.5	0.34	0.04	2.66
TOPFA*	3	1	33.3	13	13	100.0	-	-	-
Age at pregnancy									
15-24	15	0	0.0	97	1	1.0	-	-	-
25-34	121	5	4.1	913	24	2.6	1.58	0.59	4.19
35-44	124	4	3.2	676	35	5.2	0.61	0.21	1.74
Age at THR/index date**									
15-24	82	3	3.7	551	15	2.7	1.36	0.38	4.77
25-34	138	6	4.3	871	29	3.3	1.32	0.54	3.22
35-44	40	0	0.0	261	16	6.1	-	-	-
Previous pregnancies									
0	73	5	6.8	367	10	2.7	2.63	0.87	7.84
1 or more	187	4	2.1	1313	50	3.8	0.55	0.20	1.54
Rheumatoid arthritis									
Yes	103	4	3.9	7	1	14.3	0.24	0.02	1.89
No	157	5	3.2	1680	59	3.5	0.90	0.36	2.28
Implant material***									
MoM	19	2	10.5				3.93	0.76	20.2

In the THR patient group, 9 neonates and fetuses with major anomalies had 25 anomaly diagnoses, and in the reference group 60 neonates and fetuses with major anomalies had 143 anomaly diagnoses. The most common major anomalies were heart and circulatory organ anomalies, ICD-10 codes Q20 – Q28 (5 neonates/fetuses in the THR patient group and 21 in the reference group), chromosomal, Q90 – Q99 (n=2 and n=14), and musculoskeletal anomalies Q65 – Q79 (n=4 and n=12). (Table 19)

Table 19. Proportions of major congenital anomalies in births/fetuses in the THR patient group and the reference group without THR.

		Women with THR				Women without THR			
		cases		anomalies		cases		anomalies	
	ICD-10 codes	n	%	n	%	n	%	n	%
Total		9	100	25	100	60	100	143	100
Type of anomaly									
Heart and circulatory organs	Q20-Q28	5	55.6	7	28.0	21	35.0	31	21.7
Musculoskeletal	Q65-Q79	4	44.4	5	20.0	12	20.0	19	13.3
Central nervous system	Q00-Q07	2	22.2	3	12.0	11	18.3	16	11.2
Chromosomal	Q90-Q99	2	22.2	2	8.0	14	23.3	15	10.5
Genitourinary	Q50-Q56, Q60-Q64	2	22.2	2	8.0	4	6.7	7	4.9
Gastrointestinal	Q38-Q45	2	22.2	2	8.0	7	11.7	8	5.6
Facial (ear, mouth, nose, eye)	Q10-Q18, Q35-Q37	1	11.1	2	8.0	14	23.3	32	22.4
Respiratory	Q30-Q34	1	11.1	2	8.0	4	6.7	4	2.8
other	Q80-Q89	0	0.0	0	0.0	10	16.7	11	7.7

5.6 THR survival after delivery (V)

In total, 1 989 women with 2 476 THRs were included in the study. (Table 20) Of these, 111 (5.6%) women with 133 (5.4%) THRs had a delivery during the follow-up. The mean follow-up in the delivery group was 9.3 years (0-21), and the median age at the start of the follow-up was 29 years. In the reference group, 1 878 women with 2 343 THRs had no deliveries. The mean follow-up was 8.1 years (0-21), and the median age at the start of the follow-up was 40.

RA was the most common indication for THR in both groups. It was, however, more prevalent in the delivery group (47%) than in the reference group (33%) (p=0.001). Other chronic diseases were more common in the reference group. The distribution of THR fixation method or bearing-type was similar between the groups. The delivery group had 51 revisions, and 30 (59%) of the revisions were performed due to aseptic loosening. In the reference group, 645 THRs were revised, and 318 (49%) revisions were performed due to aseptic loosening.

The deliveries were analyzed and recorded per THR. During the follow-up, 170 deliveries occurred (mean of 1.3 deliveries per THR). The maximum number of deliveries per patient during the follow-up was 5. Of the deliveries, 75 (44%) were vaginal and 95 (56%) cesarean sections. Fifty women with 53 THRs had at least 1 vaginal delivery after THR, and 61 women with 80 THRs had only cesarean sections after THR. The primary THR diagnoses and revision indications were similar in the vaginal delivery group and the cesarean section group. (Table 21)

Table 20. Background characteristics of the study population (study V), types of hip prosthesis, and indications for revisions between the delivery group and the reference group.

	Delivery group		Reference group	
	n=133	%	n=2 343	%
Age at primary THR				
Mean + SD (t-test)	28.9	5.5	38.1	6.6
Median + IQR (MWU)	29.0	8.0	40.0	8.0
Age at primary THR				
Under 25	27	20.3	130	5.5
25 to 34	88	66.2	410	17.5
35 and over	18	13.5	1 803	76.9
Follow-up period (years)				
Mean + SD (t-test)	9.3	4.2	8.1	5.1
Median + IQR (MWU)	9.1	6.4	8.0	8.4
Rheumatoid arthritis	62	46.6	774	33.0
Other chronic disease**	5	3.6	208	8.9
Nulliparous at primary THR	78	63.9	778	33.0
Metal-on-metal bearing	16	12.0	390	16.6
Type of THR fixation				
Uncemented	114	85.7	1 859	79.4
Hybrid	7	5.3	237	10.1
Inverse hybrid	0	0.0	1	0.0
Cemented	12	9.0	245	10.5
Indication for THR				
Inflammatory arthritis (RA+others)	62	46.6	731	31.2
Primary osteoarthritis	12	9.0	532	22.7
Secondary arthrosis	21	15.8	363	15.5
Congenital hip luxation	22	16.6	493	21.0
Other	16	12.0	224	9.6
Revisions	51	38.3	645	27.5
Revision indications				
Aseptic loosening	30	58.8	318	49.3
Deep infection	1	2.0	11	1.7
Periprosthetic fracture	0	0.0	12	1.9
Dislocation	1	2.0	30	4.7
Pain	0	0.0	0	0.0
Others	14	27.4	193	29.9
Missing	5	9.8	81	12.5

Table 21. Comparison of primary diagnoses and revision indications in the delivery group between women with at least 1 vaginal delivery after total hip replacement (THR) to women with only cesarean sections after THR. DDH = developmental dysplasia of the hip

	Vaginal delivery after THR	Cesarean section after THR
Total no. of implants	n=53	n=80
Indication for THR		
Inflammatory arthritis	19	43
Primary osteoarthritis	4	8
Secondary arthrosis	13	8
DDH	10	12
Other	7	9
Revisions	15	36
Revision indications		
Aseptic loosening	10	20
Deep infection	1	0
Dislocation	0	1
Others	4	10
Missing	0	5

At 6 years, the implant survival rate in the delivery group was 91% (CI 85 – 96) and in the reference group 88%, (CI 87% – 90%). At 13 years, the survival rate was 50% (CI 39% – 62%) for the delivery group and 61% (CI 59% – 64%) for the reference group, respectively. (Figure 9, Table 22)

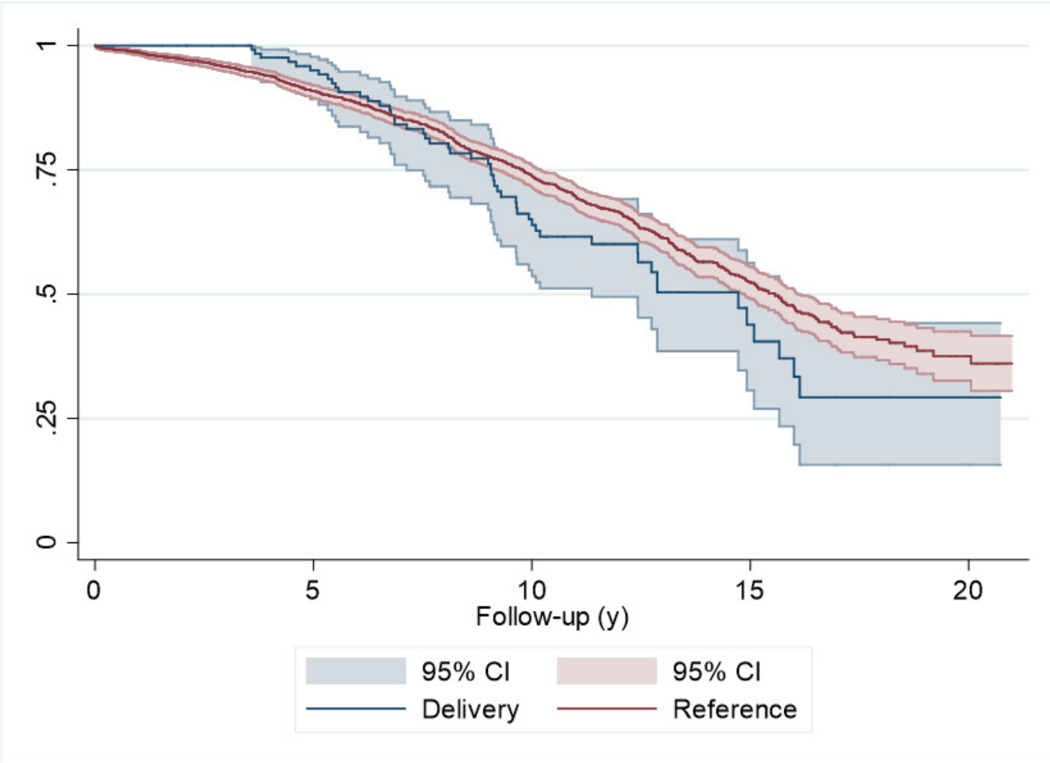


Figure 9. Kaplan Meier survival curves (with 95% confidence intervals) of primary total hip replacement among fertile-aged women aged 15 to 44 years at the time of THR having one or more deliveries after THR (delivery group) compared with no-deliveries after THR (reference group).

During the first time period (0 to 6.8 years follow-up), the adjusted Cox regression model showed no difference in the risk for revision between the delivery and the reference groups (adjusted HR 0.72, 95% CI 0.43 – 1.23; p=0.23). During the later follow-up (6.8 to 21 years), there was still no difference in adjusted HR between the groups (HR 1.12, 95% CI 0.77 – 1.62; p=0.56). Older age was associated with a decreased risk for revision during both the first and the second time periods, HR 0.97 for revision per additional year. Diagnosis of RA significantly decreased the risk for THR revision, but only during the first time period. (Table 23)

Table 22. Kaplan Meier 6- and 13-year implant survival rates with 95% confidence intervals of primary Total Hip Replacement (THR) of fertile-aged women aged 15 to 44 years at the time of THR.

	No. of Hips	No. of Revisions	No. at risk at 6 years	KM-survivorship at 6 years % (95% CI)	No. at risk at 13 years	KM-survivorship at 13 years % (95% CI)
Delivery	133	51	100	90.6 (85.3 – 95.9)	22	50.4 (39.0 – 61.8)
No delivery	2 343	645	1 411	88.4 (87.0 – 89.8)	456	61.4 (58.7 – 64.1)
Age						
15 to 30	414	148	252	87.7 (84.2 – 91.2)	75	52.2 (45.5 – 58.9)
31 to 45	2 062	548	1 260	88.7 (87.1 – 90.3)	404	62.5 (59.6 – 65.4)
THR fixation						
Cementless	1 973	625	1 325	88.6 (87.0 – 90.2)	415	59.7 (56.8 – 62.6)
Hybrid	244	23	43	85.0 (78.1 – 91.9)	5	-
Cemented	257	47	143	91.3 (87.4 – 95.2)	47	71.5 (62.9 – 80.1)
Bearings						
MoM	406	17	21	94.1 (90.8 – 97.4)	0	-
Non-MoM	2 070	679	1 490	88.5 (87.1 – 89.9)	479	60.6 (57.9 – 63.3)
Rheumatoid arthritis						
Yes	836	261	607	92.4 (90.4 – 94.4)	216	63.2 (58.9 – 67.5)
No	1 640	435	905	86.3 (84.3 – 88.3)	263	59.3 (55.8 – 62.8)

Table 23. Adjusted piecewise Cox regression survivorships of primary total hip replacement (THR) between fertile-aged women aged 15 to 44 years at the time of THR having one or more deliveries after THR (delivery group) compared with no-deliveries after THR (reference group).

	Follow-up <=6.8 years		Follow-up >6.8 years	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Delivery	**0.72 (0.43 – 1.23)**	**0.23**	**1.12 (0.77 – 1.62)**	**0.56**
Age, per year	0.97 (0.95 – 0.98)	<0.001	0.97 (0.96 – 0.99)	<0.001
Cemented stem	1.29 (0.82 – 2.03)	0.27	0.32 (0.08 – 1.27)	0.10
Cemented cup	0.64 (0.34 – 1.19)	0.16	2.09 (0.50 – 8.82)	0.32
Rheumatoid arthritis	0.49 (0.37 – 0.65)	<0.001	0.98 (0.80 – 1.20)	0.86

THR= Total Hip Replacement

HR= Hazard Ratio

95% CI= 95 percent Confidence Interval

6 DISCUSSION

6.1 Birth rate

The main finding in study I was that THR patients had lower fertility when comparing to reference individuals, in both women and men. THR patients had a lower birth rate and a lower probability of having a child after surgery. Even after taking possible confounding factors into account, THR patients still had a lower probability of having a child, and in women this difference was especially evident (for men, aHR = 0.80; for women, aHR = 0.56). Our study is the first of its kind and gives baseline information about the birth rate of offspring in both women and men who have undergone THR.

Although the birth rate was not the main aim of studies II, III, and IV, it can be interpreted from the results. All of the studies showed inferior pregnancy and birth rates among women with THR compared with women without THR. The pregnancy rate in study IV was over twice as high as in the reference group. Moreover, the available IAs were also counted in study IV. The groups were matched by age, so age should not explain the results.

Marital status did not confound the effect of THR on birth rate in our study, but it slightly modified the association. As exact information on marital status at the time of THR was not available, information on the first marriage was used and the groups were categorized as ever married or never married. Information on DM and RA diagnosis was obtained at the time of THR. DM is known to reduce fertility rates among men and women (Sjöberg et al., 2013). RA reduces female fertility compared with women without RA (Skomsvoll et al., 2001; Wallenius et al., 2011). Due to the missing information on possible changes in marital status, DM or RA, these factors were not included in the analyses as time-dependent covariates, and therefore residual confounding due to these factors is possible.

We did not have information on possible gynecological or urological procedures, or any other factors that might reduce fertility or cause infertility. Also, no information on spontaneous or induced abortions was available for this part of the study, but this was analyzed in studies II and IV where no evidence of higher IA rates was found among THR patients. The exclusion of these factors may have affected residual confounding in study I, so these results should be interpreted with caution.

We restricted the age of the study cohort to women aged from 15 to 45 and to men aged from 15 to 50 at the time of THR. Aging affects a woman's reproductive potential through menopause, but the effects of aging on the fertility of a man remain poorly defined (Johnson et al. 2015). However, men over 51 years are still of a fertile age. The exclusion of the offspring of men aged over 50 at the time of the THA may have biased our results, if the birth rate differed substantially between THA patients and reference individuals in this age group.

According to earlier studies, pregnancy and delivery can occur safely after THR (Sierra et al., 2005; Stea et al., 2007). Pregnancy and delivery are not associated with lower function of the prosthesis, and the radiographic appearance of the prosthesis is not adversely affected by pregnancy (Lally et al., 2015; McDowell & Lachiewicz, 2001; Meldrum et al., 2003; Sierra et al., 2005; Stea et al., 2007). Furthermore, pregnancy does not increase the number of early revisions of hip prostheses (Smith, M. et al., 2008), and pregnancy and delivery are not associated with a lower survival rate of hip prostheses. Furthermore, there is no increase in pregnancy-related complications in pregnancy after THR (McDowell & Lachiewicz, 2001; Smith, M. et al., 2008). In all these earlier studies (presented in Table 3), the study groups have been small and there have been no proper reference groups. In addition, no previous studies have been carried out on the birth rate of offspring of men in partnerships after THR.

One explanation for the lower birth rate in all THR patients might be a lower quality of life in THR patients than in people with no THR. It has been reported that THR patients fared worse in many areas of perceived health. (Rasanen et al., 2007) Another study showed that quality of life is similar in THR patients and in people without THR in most dimensions (Stea et al., 2007). In contrast, it has also been found that people who have a condition that may require THR suffer from a lower quality of life (Sierra et al., 2005; Stea et al., 2007). It has also been reported that THR reduces hip-related problems in the sexual life of RA patients (Baldursson & Brattström, 1979; Harmsen et al., 2016; Stern et al., 1991). Overall, THR improves quality of life compared to the pre-operational situation in many dimensions and may therefore increase birth rate as the patient's quality of life improves after surgery.

Having previously had live-born children before THR affected the birth rate after THR in both men and women. Compared with those who already had children, both patients and reference individuals with no children before surgery had a higher birth rate after surgery. While the birth rate was consistently higher in the reference population, the difference in birth rates between THR patients and their designated references was less pronounced in those individuals who had previously had live-born children. This change in birth rates can also be seen as a change in hazard ratios for a live-born child when comparing THR patients with reference individuals. This could be due to a tendency of the reference group to have reached their planned family size at a younger age because of their higher quality of life.

6.2 Induced abortions

Our study (II) showed no increase in the risk of pregnancy ending in induced abortion in women with THR compared with women in the reference group without THR. When adjusting for available and possible confounders, such as age, marital status, previous deliveries, and abortions, the risk for abortion was increased in relation to the reference group but remained borderline non-significant. More abortions were carried out due to maternal health reasons in the THR patient group than in the reference group.

No differences in IA proportions between the groups were observed when the THR patients were compared with the referents. The IA proportions in all groups were similar to the overall national abortion proportion in 2015 (14.5%). IA rates in the THR patient group were lower compared with the reference group and national means. This finding was due to the lower number of pregnancies per woman in the THR patient group. We showed in study I that women have a lower birth rate after THR compared with women without THR.

Since no previous studies have analyzed the connection between THR and IA, we had to evaluate the effect of other possible factors influencing IA risk. Women with THR had lower SES than the referents. Low SES is a risk factor for induced abortion. Women with a lower educational level or income have a higher rate of IA when compared with women with a higher educational level and income (Perez, Garcia-Subirats, Rodriguez-Sanz, Diez, & Borrell, 2010; Perez, Ruiz-Munoz, Gotsens, Cases, & Rodriguez-Sanz, 2014). Low income levels and low educational levels are risk factors for IA (Jones et al., 2002; Väisänen, 2015). The same effect was seen in our study population where blue-collar workers had a higher IA rate than persons with a higher SES. Although THR patients had lower SES, our study showed no increase in risk for IA in the THR group. However, the number of persons with missing information on SES was high in our study.

Previous IA was a high risk factor for IA in this study (Heikinheimo et al., 2009; Leppälahti et al., 2012; Väisänen & Murphy, 2014). Previous studies have verified evidence on repeat IA, where the decision to have a second IA is easier after a previous IA (Skjeldestad, 1994). The incidence of repeated IAs is decreasing, however (Laanpere et al., 2014). Providing free, long-acting reversible contraception after IA has been proven to be effective in decreasing repeat IA (Heikinheimo et al., 2008; Pohjoranta et al., 2015). After THR, women were more likely to have their first IA, which may indicate that THR might increase the IA risk.

In the THR patient group, there were more abortions both before and after THR due to maternal health indications than in the referents. Women with THR might have concerns about pregnancy, which could lead to a higher IA rate, although there is no evidence of THR complicating pregnancy or affecting pregnancy outcome (Maffulli, Del Buono, & Denaro, 2012; McDowell & Lachiewicz, 2001; Sierra et al., 2005; Stea et al., 2007). Our results could serve to reduce these concerns. The THR patients might have had more baseline diseases compared with the referents, and some diseases are known to increase IA rates. For example, women using psychotropic medication or biological RA medication have increased abortion rates (Gissler, Artama, Ritvanen, & Wahlbeck, 2010; Vinet, É et al., 2013). Asthma has also been shown to increase IA rates (Blais et al., 2013; Tata et al., 2007). This finding could not, however, be identified in our present study due to the small incidences of chronic diseases (except RA) and the information on exact medications was not available.

6.3 Deliveries

The intended modes of delivery differed between groups in study III. Women in the THR group had more elective CS and fewer trials of labor than women in the reference group. One explanation for the higher rate of elective CS could be that patients with a replaced hip opt to have elective CS because of a possible fear of damaging the THR implant and negatively affecting the delivery outcome in vaginal delivery. Earlier studies have reporter that patients with THR and their obstetricians have chosen CS because of the fear of vaginal delivery harming the implant (Meldrum et al., 2003; Ostensen, 1993). Women with congenital hip dysplasia might reportedly have a tighter pelvis that could complicate vaginal deliveries (Meldrum et al., 2003). Women in the THR group already had higher CS proportions before THR compared with the reference group, which might be explained by the underlying diseases. A German cohort study showed that women with chronic diseases were more likely to deliver by CS than healthy referents. (Kersten et al., 2014) The following chronic diseases have been shown to increase the risk for CS: pregestational DM (Berger et al., 2016), RA (Wallenius et al., 2014), obesity (Vernini et al., 2016), and epilepsy (Artama, Miia et al., 2017). It is also possible that obstetricians more often want to carry out CS due to a fear of obstetric complications among patients with THR.

The trials of labor were more likely to result in acute CS in the THR group compared with the reference group. It remains unclear whether this finding was due to possible abnormalities in cardiotocography or prolonged first or second stage labor since this information was not unfortunately available. It is also possible that not all THR patients classified as having a trial of labor were really opting for vaginal delivery. The small percentage of epidural analgesia and amniotomies after THR may be explained by the possibility that a considerable number of parturients in that group had actually planned elective CS, but it had been converted to emergency CS for reasons such as early onset of labor. Our results differ from those of the largest previous study by Sierra et al. who observed a total of 47 deliveries after THR and suggested that the percentage of CS (35.0%) in their patient series did not differ from national levels(Sierra et al., 2005). A couple of smaller patient series also reported similar CS rates compared to national levels in their studies (Lally et al., 2015; Yazici et al., 2003; Yoon, H. J. et al., 2012), while some smaller studies have reported increased rates of CS (41.1%-100%) (Meldrum et al., 2003; Ostensen, 1993; Stea et al., 2007). However, none of these previous studies have had control groups without THRs.

6.4 Neonates

The results of the study III raise the concern that adverse pregnancy outcomes are significantly more common in women after THR than women before THR or without THR. These complications included stillbirth, preterm birth, and LBW and SGA neonates.

In Finland, the national stillbirth rate has been between 3 to 5 per 1000 births for the last 30 years.(Vuori & Gissler, 2016) The stillbirth rate of the control group, as well as the patient group before THR, was similar to national levels, but in the patient group after THR it was four to five times higher. One reason for the increased stillbirth rate might be the underlying diseases of the THR patients. Two of the four women in the patient group with a stillbirth had RA. In large cohort studies, RA has been shown to increase the risk of preterm birth and SGA neonate, but not for stillbirths or perinatal mortality (Aljary et al., 2018; J.F Skomsvoll, V Baste, M Østensen, L.M Irgens, 1999; Wallenius et al., 2014). However, the prevalence of RA was also high in the patient group before THR.

There have been some reports describing the possible effects of ion release from metal-on-metal implants on fetal health. Chromium and cobalt have been shown to be toxic, but it is believed that the increased blood metal ion concentration remains below teratogenic levels. The placenta also prevents a great proportion of the ions from entering the fetal blood circulation. (Brodner et al., 2004; Novak et al., 2014; Ziaee et al., 2007) Although the concentrations of metal ions may remain below teratogenic levels, the slightly elevated fetal blood metal ion level might influence the growth of the fetus and may be involved in preterm births or stillbirths. MoM-implants gained popularity in Finland in 2000 and remained in use widely for the following 10 years. In this study, the MoM-implant THR group had a higher SGA proportion than the non-MoM group, but no other differences in pregnancy outcomes were found. We had no information available on maternal metal ion levels.

6.5 Congenital anomalies

We found in study IV that newborns after maternal THR have similar rates of congenital anomalies compared with referents without THR. According to these results, it seems safe to give birth after THR. Moreover, non-MoM implants had similar proportions of anomalies as the reference group. Since the birth rate is lower after THR (Studies I,II,III, and IV) and patients might have concerns about pregnancy after THR (Meldrum et al., 2003; Sierra et al., 2005), these findings could possibly serve to lessen these concerns.

Although women with MoM-THR had a slightly higher incidence of congenital anomalies than either the patients with non-MoM THR or referents, these differences were not statistically significant. Due to the low number of MoM patients and events in this study, however, the true effect remains unclear. MoM implants have been shown to release metal ions (Cr and Co) into the blood circulation and may be harmful to human cells (Daley et al., 2004; Hartmann et al., 2013; Langton et al., 2010). Even though the placenta prevents the majority of the ions from entering the fetal blood circulation (transfer rate for Cr 0.10-0.30 and for Co 0.46-0.61), the ion levels in the fetuses of MOM THR patients have been shown to be elevated compared with fetuses without maternal MoM THR Table 2, (Novak et al., 2014; Ziaee et al., 2007).

There have been two previous case reports in which congenital anomalies have been detected in the offspring after maternal MoM THR. The other was thought to be hereditary and had multiform congenital anomalies similar to those found in elder siblings. The other case was hypospadias. (Brodner et al., 2004; Oppermann et al., 2015) Johnson et al. contacted retrospectively 48 women aged under 40 at the time of MoM hip resurfacing. Among these women, 17 pregnancies occurred with 14 livebirths. No congenital anomalies were reported. This study also reported no problems in childhood development among these children. (Johnson et al., 2013) Based on the previous literature and the results of our study, the possible teratogenic effect of the metal-ions released from the MoM implant cannot be ruled out.

There were no major differences when the types of anomaly were compared between the groups. The most common anomaly in both groups was heart and other circulatory organ anomalies. Interestingly, neonates in the reference group seemed to have higher proportions of facial anomalies compared with the THR group. However, due to the small incidences of anomalies, the comparison of groups based on anomaly types was not statistically sound.

Since THR patients have higher incidences of juvenile RA compared with national levels, it was also taken as part of the analysis in our study. RA does not increase the risk of congenital anomalies, although some of the drugs used to treat RA have been shown to be teratogenic and are thus prohibited during pregnancy (Posfai, Banhidy, Urban, & Czeizel, 2015; Sihvonen & Pertovaara, 2019; Wallenius et al., 2014; Williams & Chakravarty, 2014). In our study, the THR and RA patients had similar rates of congenital anomalies compared with non-RA patients.

6.6 Implant survival

To the best of our knowledge, our study is the first one to assess THR implant survivorship in fertile-aged women in a large population-based study sample. Based on our results, delivery does not seem to adversely affect hip implant survivorship after primary THR.

Our results are in concordance with previous smaller studies. In their study, Sierra et al. (2005) reported that delivery after primary THR does not decrease the survival rate of the implant. They had the largest number of participants prior to our study. In total, 343 women with 420 THR were contacted and 47 of those had pregnancy ending in delivery. The survival rates for the 5- , 10- and 15-year follow-up periods, however, were calculated for the whole cohort with no comparisons made between the delivery and non-delivery groups. Our 6-year survival rate in both groups was in line with these results. Meldrum et al. (2003) had 13 hips with deliveries in their study population and reported no adverse effects for THR. Yazici et al. (2003) reported 21 THR patients with deliveries and no decrease in the survival rate of the THR. All these studies were retrospective with alternative response rates (30 to 75%). McDowell and Lachiewicz (2001) reported 5 women with 7 uncemented THRs having deliveries and compared them with matched referents, and no differences between survival or hip functions were reported. Our study is the only one to report a slight but not statistically significant decrease in implant survival rate in the Kaplan Meier analysis after delivery.

Cesarean section (CS) rate was markedly increased in the delivery group compared to the overall CS rate in Finland. There have been previous reports in which it has been suggested that women with dysplastic hips have smaller pelvic diameters, and they therefore tend to have CS (Sierra et al. 2005; Stea et al. 2007). In our study, developmental dysplasia of the hip was an equally common indication for THR in women who only had cesarean sections after THR as in those who delivered vaginally after THR. Also, there were no differences in revision indications between them. The reason for the very high CS rate in the delivery group remains unknown. We can only speculate that the presence of THR may have affected the patients' and/or the physicians' choice of delivery. However, it did not have any effect of THR survival rates.

Age was the only statistically significant variable that negatively affected THR implant survivorship. The median age of the delivery group at the start of the follow-up was 29 years compared with the reference group´s 40 years. Previously, only Sierra et al. (2005) have applied the Cox regression model to analyze implant survivorship after delivery. In their model, delivery seemed to decrease THR survivorship, but once age at the time of primary THR was taken as part of the model, no further differences between the delivery group and the reference group were obtained. Previous non-delivery related THR survival studies have reported similar findings of weaker implant survivorship in younger patients (Dorr et al. 1994; Nam et al. 2016; Tsukanaka et al. 2016). In particular, very young patients under 30 years have been reported to have had decreased THR survivorship (Mohaddes et al. 2019). This finding is probably because of higher activity levels. (Adelani et al., 2013; Dorr et al., 1994) Our survival rates were slightly lower compared to a recent study by Mohaddes et al. (2019) in which the 15-year THR survival rate for patients aged under 30 at the time of THR was 76%.

In young patients (<50 years or less), indications for THR differ in comparison with older patients (+50 years). In younger patients, inflammatory arthritis and developmental hip diseases are more common, and primary osteoarthritis is rare (Adelani et al. 2013). Developmental dysplasia of the hip decreases the survival of the hip prosthesis in young patients (Havelin et al. 2000; Tsukanaka et al. 2016). There have been controversial results regarding the survival of the THR in RA patients. Some studies have suggested decreased THR survivorship, more common radiographic findings indicating implant failure, poorer function, and increased mortality among patients with RA (Creighton et al. 1998; Goodman et al. 2014; Havelin et al. 2000; Schrama et al. 2015; Singh & Lewallen 2013; Tang & Chiu 2001). Inflammatory arthritis as primary diagnosis for THR may also increase revisions due to deep infections (Dale et al. 2012). Previous large national cohort studies have, however, shown no decrease in THR survival due to RA (Eskelinen et al. 2006; Furnes et al. 2001; Havelin et al. 2000). Because of the high prevalence of RA among young patients, it was taken as part of the Cox model. In our model, RA did not decrease THR survival. Indeed, it seemed patients with RA had better results during the first follow-up period (< 6.8 years). A similar finding was seen in a previous THR and delivery study, where Serra et al. (2005) found no decrease in the survival of hips operated due to RA diagnosis in their step-by-step Cox results.

6.7 Strengths and limitations

6.7.1 Strengths of the study

Overall, the main strengths of this study are the following:

First, a long study period provided us with by far the largest population of fertile-aged THR patients and increased the accuracy of our analysis.

Second, our study was a nationwide study that represented the whole country instead of a local population from one hospital region. This makes our results more generalizable, although the events in this study were rare.

Third, the register-based approach eliminates any possible recall and reporting bias. For example, the indications of the surgeries are known, and the dates of the events are exact, which allowed us to calculate reliable follow-up periods if needed. Additionally, the data for the registers are gathered as structured which increases the reliability.

Fourth, the overall quality and completeness of the registers has been proven to be excellent (Heino et al., 2018; THL, 2018c; THL, 2018d).

Fifth, the combination of the different registers enabled the unique study design.

Sixth, we were able to compare birth rate, IAs, pregnancies, deliveries, and neonates both before and after THR with a reference group.

6.7.2 Main limitations of the study

There are also some limitations to our results in this study, which are mainly due to the register-based study design. Also, throughout the study, we had to analyze our results with caution, since the THR patient group had much higher proportion of RA. Due this reason, the RA has been taken as part of the analyses to control the bias of confounding by indication. This means, that the results might be due the underlying disease that has led to THR and not due the THR itself.

First, although the register data have excellent overall coverage and completeness, there were, however, a few key variables in these registers with poor levels of content. For example, in study II, SES was only available for 34.1% of the participants, and in study III, information on previous preterm deliveries or previous SGA children was not available. Moreover, no information on body mass index was recorded before 2004 and the register data had only contained information on 1-minute Apgar-scores, since 5-minute scores only became part of the register in 2004. Also, delivery stage durations were not found in most of the cases, since they also only became part of the register in 2004. Information on marital status in the studies was categorized as never married or ever married and was not fully time specific for our study period.

Second, the information on long-term diseases was gathered from the medical reimbursement statistics instead of from hospital discharge data or medical treatment data. Everyone with at least one reimbursement period due to disease during their lifetime is included in the register. The reimbursement is based on the diagnosis of DM or RA, and therefore DM or RA medications prescribed for other indications are not included in the reimbursements for these chronic diseases. Furthermore, it is possible that some of the subjects with recently diagnosed DM or RA had not yet been included in the register. Also, some DM patients, such as diabetes type-II patients, are not reimbursed for medication due to the low cost of basic DM medications.

Third, the long study period. During the 20-year period, delivery methods changed. The use of forceps has decreased, whereas the use of vacuum extraction in deliveries has increased. Also, the medications used for the treatment of RA have changed during this period, and especially when biological medications came in to use in the early 2000s. Trends in THR surgery have also changed back and forth during the 20-year period of the study.

Fourth, our study period did not perfectly match with the main years of use of MoM implants. MoM implants gained popularity in Finland in the early 2000s and were widely used until 2012. These implants were known to have poorer survival rates than non-MoM implants (Furnes, Ove et al., 2014; Smith, A. J., Dieppe, Vernon, Porter, & Blom, 2012b; Varnum et al., 2015). However, this could not be seen in the results of the current study with a rather short follow-up period for MoM implants. Also, an even longer study follow-up would have aided us in evaluating more reliably whether MoM implants would potentially affect the incidence of anomalies.

Fifth, the low number of events in study IV decreased the generality of our results and meant a lack of statistical power. Since THR is a relatively rare operation in younger fertile women, the number of pregnancies as well as the number of the anomalies remained quite small.

Sixth, there was a lack of PROMs in study V. Therefore, we had to focus solely on THR survival, and function after delivery could not have been analyzed in a larger setting.

6.8 Future studies

According to our results, future research should analyze the effects of maternal THR on fetal growth and adverse pregnancy outcomes in a larger multinational register-based cohort study. Another possible future topic could be the effect of MoM implants on neonate outcome and risk of congenital anomalies. Such a multinational register-based cohort study would have a longer study period and a larger study population and initial participant inclusion to address the topic more precisely.

7 SUMMARY AND CONCLUSIONS

The goal of this study to provide new information on reproductive health after THR in fertile-aged patients. We conducted a nationwide register-based cohort study for the period 1987 to 2007 to evaluate birth rate, induced abortions rate, deliveries, neonate outcome, and congenital anomalies after THR compared with a reference group without THR. Further, the survivorship of the hip implant after delivery was analyzed. The following are the principal findings and conclusions of each study:

i. THR patients had a lower birth rate and probability of having a child after surgery, even after taking possible confounders into account.
ii. The THR patient group had higher induced abortion proportions compared with the reference group before and after THR. After THR, patients were not more likely to have a pregnancy ending in induced abortion. This finding remained statistically insignificant after adjusting with possible confounders.
iii. According to the findings of this study, adverse pregnancy outcomes (preterm birth, LBW, SGA, and stillbirth) are more common in women who have undergone THR. As a result, such women are more likely to have elective and emergency cesarean sections after THR.
iv. Maternal THR does not increase the risk of congenital anomaly in neonates. Further studies with larger study populations and longer follow-up are needed to confirm our finding of unelevated risk for anomalies in the offspring of women having undergone MoM THR.
v. Based on the findings of this nationwide study delivery does not seem to decrease THR implant survivorship. Hence, women should not be afraid of or try to avoid becoming pregnant after THR.

8 ACKNOWLEDGEMENTS

This study was carried out at COXA Hospital for Joint Replacement and Tampere University.

I could have never imagined how much I would learn by making this thesis. I had the privilege of working with skillful scientists and great persons. I had three excellent supervisors in this thesis, and I would like to express my deepest gratitude to all of you. Docent Antti Eskelinen, Docent Miia Artama and Docent Eerik Skyttä guided me with wisdom and calmness during these years. I appreciate that you all took the countless deadlines seriously and gave me excellent feedback and endless support all the time. You were always reachable and ready to help. Special thanks to Antti, as the responsible supervisor, who I bombed the most with questions and tasks.

My gratitude goes to Heini Huhtala for being an amazing biostatistician and mental support. I think we were lucky to have the best statistician in our group. At first our meetings were more about statistics, but during these years the meetings evolved more into discussion sessions, in which at some point I just confirmed that I have done the right things.

I would also like to thank Docent Jukka Uotila for collaboration in the III publication of this thesis. It was important to have an experienced obstetrician as part of the project. My relationship with Jukka started in the second year of med school when Jukka supervised my MD thesis together with Docent Outi Tammela and PhD Riitta Ojala. Thank you for exciting me on making research.

Thank you for the official pre-examiners of this thesis, Docent Veli-Matti Ulander and Docent Riitta Luoto, for their evaluation of the manuscript and criticism, which helped to improve it. Thank you for the language correction of this thesis, Mr. Peter Heath. Peter was extremely fast and gave instructive and positive comments.

I want to thank my friends for great friendship and amazing moments during our years of studying. Many of my friends are PhD students as well, which meant excellent peer support.

I love my family and I want to thank Matti and Leila for being the best parents I could imagine and for encouraging me to study and educate myself. I have wonderful sisters Emmi and Eveliina, who have been my support always and Emmi's husband Joonas, who has been a big brother for me for 15 years already. Eeli and Enna, the little ones, you cheer me every time.

Finally, the biggest Thank You and my deepest gratitude goes to my love, Emma. You have been supportive and patient with my projects, work and studies. That hasn't always been easy, but you have always given me support and room to do my things. Thank you for your love and support. There are two stars for us in the sky.

Mikkeli, October 2019

Ilari Kuitunen

9 REFERENCES

References

A P Davies, A Sood, A C Lewis, R Newson, I D Learmonth, & C P Case. (2005). Metal-specific differences in levels of DNA damage caused by synovial fluid recovered at revision arthroplasty. *The Journal of Bone and Joint Surgery. British Volume, 87*(10), 1439-1444. doi:10.1302/0301-620X.87B10.16541

AAOS. (2012). *Information statement: Current concerns with metal-on-metal hip arthroplasty.* (). Retrieved from https://www.aaos.org/uploadedFiles/PreProduction/About/Opinion_Statements/advistmt/1035%20Current%20Concerns%20with%20Metal-on-Metal%20Hip%20Arthroplasty.pdf

Adelani, M. A., Keeney, J. A., Palisch, A., Fowler, S. A., & Clohisy, J. C. (2013). Has total hip arthroplasty in patients 30 years or younger improved? A systematic review. *Clinical Orthopaedics & Related Research, 471*(8), 2595-2601. doi://dx.doi.org/10.1007/s11999-013-2975-x

Ali, Z., Hansen, A. V., & Ulrik, C. S. (2016). Exacerbations of asthma during pregnancy: Impact on pregnancy complications and outcome. *Journal of Obstetrics and Gynaecology: The Journal of the Institute of Obstetrics and Gynaecology, 36*(4), 455-461. doi:10.3109/01443615.2015.1065800

Aljary, H., Czuzoj-Shulman, N., Spence, A. R., & Abenhaim, H. A. (2018). Pregnancy outcomes in women with rheumatoid arthritis: A retrospective population-based cohort study. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* , 1-7. doi:10.1080/14767058.2018.1498835

Anne-Dorthe Feldthusen, Palle L. Pedersen, Jacob Larsen, Tina Toft Kristensen, Christina Ellervik, & Jan Kvetny. (2015). Impaired fertility associated with subclinical hypothyroidism and thyroid autoimmunity: The danish general suburban population study. *Journal of Pregnancy, 2015*, 132718-6. doi:10.1155/2015/132718

AOANJRR. (2019). Australian orthopaedic association national joint replacement registry - annual report 2018. *Australian Orthopaedic Association National Joint Replacement Registry,* Retrieved from https://aoanjrr.sahmri.com/annual-reports-2018

Artama, M., Auvinen, A., Raudaskoski, T., Isojärvi, I., & Isojärvi, J. (2005). Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. *Neurology, 64*(11), 1874-1878. doi:10.1212/01.WNL.0000163771.96962.1F

Artama, M., Isojärvi, J. I. T., Raitanen, J., & Auvinen, A. (2004). Birth rate among patients with epilepsy: A nationwide population-based cohort study in finland. *American Journal of Epidemiology, 159*(11), 1057-1063. doi:10.1093/aje/kwh140

Artama, M., Braumann, J., Raitanen, J., Uotila, J., Gissler, M., Isojärvi, J., & Auvinen, A. (2017). Women treated for epilepsy during pregnancy: Outcomes from a nationwide population-based cohort study. *Acta Obstetricia Et Gynecologica Scandinavica, 96*(7), 812-820. doi:10.1111/aogs.13109

Artama, M., Gissler, M., Malm, H., & Ritvanen, A. (2011). Nationwide register-based surveillance system on drugs and pregnancy in finland 1996-2006. *Pharmacoepidemiology and Drug Safety, 20*(7), 729-738. doi:10.1002/pds.2159

Asadipooya, K., Graves, L., & Greene, L. W. (2017). Transient osteoporosis of the hip: Review of the literature. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 28*(6), 1805-1816. doi:10.1007/s00198-017-3952-0

Atrey, A., Ward, S. E., Khoshbin, A., Hussain, N., Bogoch, E., Schemitsch, E. H., & Waddell, J. P. (2017). Ten-year follow-up study of three alternative bearing surfaces used in total hip arthroplasty in young patients: A prospective randomised controlled trial. *The Bone & Joint Journal, 99-B*(12), 1590-1595. doi:10.1302/0301-620X.99B12.BJJ-2017-0353.R1

Aune, D., Saugstad, O. D., Henriksen, T., & Tonstad, S. (2014). Maternal body mass index and the risk of fetal death, stillbirth, and infant death: A systematic review and meta-analysis. *Jama, 311*(15), 1536-1546. doi:10.1001/jama.2014.2269

Baldursson, H., & Brattström, H. (1979). Sexual difficulties and total hip replacement in rheumatoid arthritis. *Scandinavian Journal of Rheumatology, 8*(4), 214-216.

Bankston, A. B., Faris, P. M., Keating, E. M., & Ritter, M. A. (1993). Polyethylene wear in total hip arthroplasty in patient-matched groups. A comparison of stainless steel, cobalt chrome, and titanium-bearing surfaces. *The Journal of Arthroplasty, 8*(3), 315-322.

Bateman, B. T., Huybrechts, K. F., Fischer, M. A., Seely, E. W., Ecker, J. L., Oberg, A. S., . . . Hernandez-Diaz, S. (2015). Chronic hypertension in pregnancy and the risk of congenital malformations: A cohort study. *American Journal of Obstetrics and Gynecology, 212*(3), 14. doi:10.1016/j.ajog.2014.09.031

Beaulieu, J. G., Razzano, C. D., & Levine, R. B. (1976). Transient osteoporosis of the hip in pregnancy. *Clinical Orthopaedics and Related Research,* (115), 165-168.

Becerra, J. E., Khoury, M. J., Cordero, J. F., & Erickson, J. D. (1990). Diabetes mellitus during pregnancy and the risks for specific birth defects: A population-based case-control study. *Pediatrics, 85*(1), 1-9.

Beksaç, B., Salas, A., González Della Valle, A., & Salvati, E. A. (2009). Wear is reduced in THA performed with highly cross-linked polyethylene. *Clinical*

Orthopaedics and Related Research, 467(7), 1765-1772. doi:10.1007/s11999-008-0661-1

Berger, H., Gagnon, R., Sermer, M., Basso, M., Bos, H., Brown, R. N., . . . Walsh, J. D. (2016). Diabetes in pregnancy. *Journal of Obstetrics and Gynaecology Canada: JOGC = Journal D'Obstetrique Et Gynecologie Du Canada: JOGC, 38*(7), 679.e1. doi:10.1016/j.jogc.2016.04.002

Bhardwaj, A., & Nagandla, K. (2014). Musculoskeletal symptoms and orthopaedic complications in pregnancy: Pathophysiology, diagnostic approaches and modern management. *Postgraduate Medical Journal, 90*(1066), 450-460. doi://dx.doi.org/10.1136/postgradmedj-2013-132377

Bisseling, P., Tan, T., Lu, Z., Campbell, P. A., & van Susante, Job L C. (2013). The absence of a metal-on-metal bearing does not preclude the formation of a destructive pseudotumor in the hip—a case report. *Acta Orthopaedica, 84*(4), 437-441. doi:10.3109/17453674.2013.823590

Blais, L., Kettani, F., & Forget, A. (2013). Relationship between maternal asthma, its severity and control and abortion. *Human Reproduction (Oxford, England), 28*(4), 908-915. doi:10.1093/humrep/det024

Boot, C. L., Heyligers, I. C., & Heins, K. F. (2003). Pregnancy and delivery after revised total hip replacement. *Orthopedics, 26*(8), 813-814.

Bosker, B. H., Ettema, H. B., Boomsma, M. F., Kollen, B. J., Maas, M., & Verheyen, C. C. P. M. (2012). High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: A prospective cohort study. *The Journal of Bone and Joint Surgery. British Volume, 94*(6), 755-761. doi:10.1302/0301-620X.94B6.28373

Bowden, A. P., Barrett, J. H., Fallow, W., & Silman, A. J. (2001). Women with inflammatory polyarthritis have babies of lower birth weight. *The Journal of Rheumatology, 28*(2), 355-359.

Breton, M. -., Beauchesne, M. -., Lemière, C., Rey, E., Forget, A., & Blais, L. (2009). Risk of perinatal mortality associated with asthma during pregnancy. *Thorax, 64*(2), 101-106. doi:10.1136/thx.2008.102970

Brewer, C. J., & Balen, A. H. (2010). The adverse effects of obesity on conception and implantation. *Reproduction (Cambridge, England), 140*(3), 347-364. doi:10.1530/REP-09-0568

Brodner, W., Grohs, J. G., Bancher-Todesca, D., Dorotka, R., Meisinger, V., Gottsauner-Wolf, F., & Kotz, R. (2004). Does the placenta inhibit the passage of chromium and cobalt after metal-on-metal total hip arthroplasty?. *Journal of Arthroplasty, 19*(8 Suppl 3), 102-106.

Bromley, R. L., Weston, J., & Marson, A. G. (2017). Maternal use of antiepileptic agents during pregnancy and major congenital malformations in children. *Jama, 318*(17), 1700-1701. doi:10.1001/jama.2017.14485

Broughton, D. E., & Moley, K. H. (2017). Obesity and female infertility: Potential mediators of obesity's impact. *Fertility and Sterility, 107*(4), 840-847. doi:10.1016/j.fertnstert.2017.01.017

Brouwer, J., Fleurbaaij, R., Hazes, J. M. W., Dolhain, Radboud J. E. M., & Laven, J. S. E. (2017). Subfertility in women with rheumatoid arthritis and the outcome of fertility assessments. *Arthritis Care & Research, 69*(8), 1142-1149. doi:10.1002/acr.23124

Brouwer, J., Hazes, J. M. W., Laven, J. S. E., & Dolhain, Radboud J. E. M. (2015). Fertility in women with rheumatoid arthritis: Influence of disease activity and medication. *Annals of the Rheumatic Diseases, 74*(10), 1836-1841. doi:10.1136/annrheumdis-2014-205383

Bullinger, L. R. (2017). The effect of minimum wages on adolescent fertility: A nationwide analysis. *American Journal of Public Health, 107*(3), 447-452. doi:10.2105/AJPH.2016.303604

Campbell, J., Rajaee, S., Brien, E., & Paiement, G. D. (2017). Inflammatory pseudotumor after ceramic-on-ceramic total hip arthroplasty. *Arthroplasty Today, 3*(2), 83-87. doi:10.1016/j.artd.2016.11.006

Carli, A., Reuven, A., Zukor, D. J., & Antoniou, J. (2011). Adverse soft-tissue reactions around non-metal-on-metal total hip arthroplasty - a systematic review of the literature. *Bulletin of the NYU Hospital for Joint Diseases, 69 Suppl 1*, 47.

Case, C. P., Ellis, L., Turner, J. C., & Fairman, B. (2001). Development of a routine method for the determination of trace metals in whole blood by magnetic sector inductively coupled plasma mass spectrometry with particular relevance to patients with total hip and knee arthroplasty. *Clinical Chemistry, 47*(2), 275-280.

Chandrasekaran, S., & Neal-Perry, G. (2017). Long-term consequences of obesity on female fertility and the health of the offspring. *Current Opinion in Obstetrics & Gynecology, 29*(3), 180-187. doi:10.1097/GCO.0000000000000364

Chang, J. (2014). Future bearing surfaces in total hip arthroplasty. *Clinics in Orthopedic Surgery, 6*(1), 110-116. doi:10.4055/cios.2014.6.1.110

Charbonnier, C., Chagué, S., Ponzoni, M., Bernardoni, M., Hoffmeyer, P., & Christofilopoulos, P. (2014). Sexual activity after total hip arthroplasty: A motion capture study. *The Journal of Arthroplasty, 29*(3), 640-647. doi:10.1016/j.arth.2013.07.043

Charnley, J., & Halley, D. K. (1975). Rate of wear in total hip replacement. *Clinical Orthopaedics and Related Research,* (112), 170-179.

Charnley, J. (1961). ARTHROPLASTY OF THE HIP: A new operation. *The Lancet, 277*(7187), 1129-1132. doi:10.1016/S0140-6736(61)92063-3

Charnley, J. (1964). A clean-air operating enclosure. *Bjs, 51*(3), 202-205. doi:10.1002/bjs.1800510309

The classic. metal hip joint. A case report. by austin T. moore and harold R. bohlman. 1943. (1983). *Clinical Orthopaedics and Related Research,* (176), 3-6.

Clayton, R. A. E., Beggs, I., Salter, D. M., Grant, M. H., Patton, J. T., & Porter, D. E. (2008). Inflammatory pseudotumor associated with femoral nerve palsy following metal-on-metal resurfacing of the hip. A case report. *The Journal of*

Bone and Joint Surgery. American Volume, 90(9), 1988-1993. doi:10.2106/JBJS.G.00879

Cleland, K., Peipert, J. F., Westhoff, C., Spear, S., & Trussell, J. (2011). Family planning as a cost-saving preventive health service. *The New England Journal of Medicine, 364*(18), e37. doi:10.1056/NEJMp1104373

Clohisy, J. C., Calvert, G., Tull, F., McDonald, D., & Maloney, W. J. (2004). Reasons for revision hip surgery: A retrospective review. *Clinical Orthopaedics and Related Research,* (429), 188-192.

Cnudde, P., Nemes, S., Bülow, E., Timperley, J., Malchau, H., Kärrholm, J., Rolfson, O. (2018). Trends in hip replacements between 1999 and 2012 in sweden. *Journal of Orthopaedic Research, 36*(1), 432-442. doi:10.1002/jor.23711

Colstrup, M., Mathiesen, E. R., Damm, P., Jensen, D. M., & Ringholm, L. (2013). Pregnancy in women with type 1 diabetes: Have the goals of st. vincent declaration been met concerning foetal and neonatal complications? *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 26*(17), 1682-1686. doi:10.3109/14767058.2013.794214

Cooke-Hubley S, Kirby BJ, Valcour JE, Mugford G, Adachi JD, Kovacs CS. Spine bone mineral density increases after 6 months of exclusive lactation, even in women who keep breastfeeding. *Arch Osteoporos.* 2017 Aug 16;12(1):73. doi: 10.1007/s11657-017-0368-6.

Courpied, J., & Caton, J. H. (2011). Total hip arthroplasty, state of the art for the 21st century. *International Orthopaedics, 35*(2), 149-150. doi:10.1007/s00264-011-1207-9

Dahlstrand, H., Stark, A., Wick, M. C., Anissian, L., Hailer, N. P., & Weiss, R. J. (2017). Comparison of metal ion concentrations and implant survival after total hip arthroplasty with metal-on-metal versus metal-on-polyethylene articulations. *Acta Orthopaedica, 88*(5), 490-495. doi:10.1080/17453674.2017.1350370

Daley, B., Doherty, A. T., Fairman, B., & Case, C. P. (2004). Wear debris from hip or knee replacements causes chromosomal damage in human cells in tissue culture. *The Journal of Bone and Joint Surgery. British Volume, 86*(4), 598-606.

Daniel, J., Ziaee, H., Pradhan, C., Pynsent, P. B., & McMinn, D. J. W. (2007). Blood and urine metal ion levels in young and active patients after birmingham hip resurfacing arthroplasty: Four-year results of a prospective longitudinal study. *The Journal of Bone and Joint Surgery. British Volume, 89*(2), 169-173. doi:10.1302/0301-620X.89B2.18519

D'Antonio, J. A., Capello, W. N., & Naughton, M. (2012). Ceramic bearings for total hip arthroplasty have high survivorship at 10 years. *Clinical Orthopaedics and Related Research, 470*(2), 373-381. doi:10.1007/s11999-011-2076-7

D'Antonio, J. A., Capello, W. N., & Naughton, M. (2014). High survivorship with a titanium-encased alumina ceramic bearing for total hip arthroplasty. *Clinical*

Orthopaedics and Related Research, 472(2), 611-616. doi:10.1007/s11999-013-2943-5
De Boeck, M., Kirsch-Volders, M., & Lison, D. (2003). Cobalt and antimony: Genotoxicity and carcinogenicity. *Mutation Research, 533*(1-2), 135-152.
De Boeck, M., Lombaert, N., De Backer, S., Finsy, R., Lison, D., & Kirsch-Volders, M. (2003). In vitro genotoxic effects of different combinations of cobalt and metallic carbide particles. *Mutagenesis, 18*(2), 177-186.
Delaunay, C., Petit, I., Learmonth, I. D., Oger, P., & Vendittoli, P. A. (2010). Metal-on-metal bearings total hip arthroplasty: The cobalt and chromium ions release concern. *Orthopaedics & Traumatology, Surgery & Research: OTSR, 96*(8), 894-904. doi:10.1016/j.otsr.2010.05.008
deSouza, R., Wallace, D., Costa, M. L., & Krikler, S. J. (2012). Transplacental passage of metal ions in women with hip resurfacing: No teratogenic effects observed. *Hip International, 22*(1), 96-99.
Devane, P. A., Horne, J. G., Ashmore, A., Mutimer, J., Kim, W., & Stanley, J. (2017). Highly cross-linked polyethylene reduces wear and revision rates in total hip arthroplasty: A 10-year double-blinded randomized controlled trial. *The Journal of Bone and Joint Surgery. American Volume, 99*(20), 1703-1714. doi:10.2106/JBJS.16.00878
Dixon, T., Shaw, M., Ebrahim, S., & Dieppe, P. (2004). Trends in hip and knee joint replacement: Socioeconomic inequalities and projections of need. *Annals of the Rheumatic Diseases, 63*(7), 825-830. doi:10.1136/ard.2003.012724
Dobbs, H. S., & Minski, M. J. (1980). Metal ion release after total hip replacement. *Biomaterials, 1*(4), 193-198.
Dribe, M., Breschi, M., Gagnon, A., Gauvreau, D., Hanson, H. A., Maloney, T. N., . . . Vézina, H. (2017). Socioeconomic status and fertility decline: Insights from historical transitions in europe and north america. *Population Studies, 71*(1), 3-21. doi:10.1080/00324728.2016.1253857
Ehrenberg, H. M., Durnwald, C. P., Catalano, P., & Mercer, B. M. (2004). The influence of obesity and diabetes on the risk of cesarean delivery. *American Journal of Obstetrics and Gynecology, 191*(3), 969-974. doi:10.1016/j.ajog.2004.06.057
Eidem, I., Vangen, S., Hanssen, K. F., Vollset, S. E., Henriksen, T., Joner, G., & Stene, L. C. (2011). Perinatal and infant mortality in term and preterm births among women with type 1 diabetes. *Diabetologia, 54*(11), 2771-2778. doi:10.1007/s00125-011-2281-7
Eidem, I., Stene, L. C., Henriksen, T., Hanssen, K. F., Vangen, S., Vollset, S. E., & Joner, G. (2010). Congenital anomalies in newborns of women with type 1 diabetes: Nationwide population-based study in norway, 1999-2004. *Acta Obstetricia Et Gynecologica Scandinavica, 89*(11), 1403-1411. doi:10.3109/00016349.2010.518594
Ekman, E., Laaksonen, I., Eskelinen, A., Pulkkinen, P., Pukkala, E., & Mäkelä, K. (2018). Midterm risk of cancer with metal-on-metal hip replacements not

increased in a finnish population. *Acta Orthopaedica, 89*(5), 575-579. doi:10.1080/17453674.2018.1487202

Eudy, A. M., McDaniel, G., & Clowse, M. E. B. (2018). Pregnancy in rheumatoid arthritis: A retrospective study. *Clinical Rheumatology, 37*(3), 789-794. doi:10.1007/s10067-017-3939-4

Evans, E. M., Freeman, M. A., Miller, A. J., & Vernon-Roberts, B. (1974). Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. *The Journal of Bone and Joint Surgery. British Volume, 56-B*(4), 626-642.

Flenady, V., Koopmans, L., Middleton, P., Frøen, J. F., Smith, G. C., Gibbons, K., . . . Ezzati, M. (2011). Major risk factors for stillbirth in high-income countries: A systematic review and meta-analysis. *Lancet (London, England), 377*(9774), 1331-1340. doi:10.1016/S0140-6736(10)62233-7

Flugsrud, G. B., Nordsletten, L., Espehaug, B., Havelin, L. I., & Meyer, H. E. (2007). The effect of middle-age body weight and physical activity on the risk of early revision hip arthroplasty: A cohort study of 1,535 individuals. *Acta Orthopaedica, 78*(1), 99-107. doi:10.1080/17453670610013493

Fritzsche, J., Borisch, C., & Schaefer, C. (2012). Case report: High chromium and cobalt levels in a pregnant patient with bilateral metal-on-metal hip arthroplasties. *Clinical Orthopaedics & Related Research, 470*(8), 2325-2331.

Fuchs, S., & Wieder, J. (2000). [Survival rate of the cemented charnley total hip endoprosthesis and modifying parameters]. *Biomedizinische Technik. Biomedical Engineering, 45*(12), 362-369.

Fullston, T., McPherson, N. O., Zander-Fox, D., & Lane, M. (2017). The most common vices of men can damage fertility and the health of the next generation. *The Journal of Endocrinology, 234*(2), F6. doi:10.1530/JOE-16-0382

Furnes, O., Lie, S. A., Espehaug, B., Vollset, S. E., Engesaeter, L. B., & Havelin, L. I. (2001). Hip disease and the prognosis of total hip replacements. A review of 53,698 primary total hip replacements reported to the norwegian arthroplasty register 1987-99. *The Journal of Bone and Joint Surgery. British Volume, 83*(4), 579-586.

Furnes, O., Paxton, E., Cafri, G., Graves, S., Bordini, B., Comfort, T., . . . Sedrakyan, A. (2014). Distributed analysis of hip implants using six national and regional registries: Comparing metal-on-metal with metal-on-highly cross-linked polyethylene bearings in cementless total hip arthroplasty in young patients. *The Journal of Bone and Joint Surgery. American Volume, 96 Suppl 1*, 25-33. doi:10.2106/JBJS.N.00459

Gade, E. J., Thomsen, S. F., Lindenberg, S., Kyvik, K. O., Lieberoth, S., & Backer, V. (2014). Asthma affects time to pregnancy and fertility: A register-based twin study. *The European Respiratory Journal, 43*(4), 1077-1085. doi:10.1183/09031936.00148713

Gade, E. J., Thomsen, S. F., Lindenberg, S., & Backer, V. (2016). Fertility outcomes in asthma: A clinical study of 245 women with unexplained infertility. *The*

European Respiratory Journal, 47(4), 1144-1151. doi:10.1183/13993003.01389-2015

Gaillard, R., Durmuş, B., Hofman, A., Mackenbach, J. P., Steegers, E. A. P., & Jaddoe, V. W. V. (2013). Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. *Obesity (Silver Spring, Md.), 21*(5), 1046-1055. doi:10.1002/oby.20088

Galindo, A., Burguillo, A. G., Azriel, S., & Fuente, P. d. l. (2006). Outcome of fetuses in women with pregestational diabetes mellitus. *Journal of Perinatal Medicine, 34*(4), 323-331. doi:10.1515/JPM.2006.062

Gallo, J., Raska, M., Mrázek, F., & Petrek, M. (2008). Bone remodeling, particle disease and individual susceptibility to periprosthetic osteolysis. *Physiological Research, 57*(3), 339-349.

Gandhi, J., Dagur, G., Warren, K., Smith, N. L., Sheynkin, Y. R., Zumbo, A., & Khan, S. A. (2017). The role of diabetes mellitus in sexual and reproductive health: An overview of pathogenesis, evaluation, and management. *Current Diabetes Reviews, 13*(6), 573-581. doi:10.2174/1573399813666161122124017

Garne, E., Hansen, A. V., Morris, J., Zaupper, L., Addor, M., Barisic, I., . . . Dolk, H. (2015). Use of asthma medication during pregnancy and risk of specific congenital anomalies: A european case-malformed control study. *The Journal of Allergy and Clinical Immunology, 136*(6), 1502.e7. doi:10.1016/j.jaci.2015.05.043

Gissler, M., Artama, M., Ritvanen, A., & Wahlbeck, K. (2010). Use of psychotropic drugs before pregnancy and the risk for induced abortion: Population-based register-data from finland 1996-2006. *BMC Public Health, 10*, 383.

Gomez, P. F., & Morcuende, J. A. (2005). Early attempts at hip arthroplasty. *The Iowa Orthopaedic Journal, 25*, 25-29. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1888777/

Goodman, S. B. (2007). Wear particles, periprosthetic osteolysis and the immune system. *Biomaterials, 28*(34), 5044-5048. doi:10.1016/j.biomaterials.2007.06.035

Guiahi, M., Schiller, G., Sheeder, J., & Teal, S. (2015). Safety of first-trimester uterine evacuation in the outpatient setting for women with common chronic conditions. *Contraception, 92*(5), 453-457. doi:10.1016/j.contraception.2015.07.005

Gupta, J. K., Sood, A., Hofmeyr, G. J., & Vogel, J. P. (2017). Position in the second stage of labour for women without epidural anaesthesia. *The Cochrane Database of Systematic Reviews, 5*, CD002006. doi:10.1002/14651858.CD002006.pub4

Gyllenberg, F. K., Saloranta, T. H., But, A., Gissler, M., & Heikinheimo, O. (2018). Induced abortion in a population entitled to free-of-charge long-acting reversible contraception. *Obstetrics and Gynecology, 132*(6), 1453-1460. doi:10.1097/AOG.0000000000002966

Hailer, N. P., Garellick, G., & Kärrholm, J. (2010). Uncemented and cemented primary total hip arthroplasty in the swedish hip arthroplasty register. *Acta Orthopaedica, 81*(1), 34-41. doi:10.3109/17453671003685400

Halvorsen V, Fenstad AM, Engesæter LB, Nordsletten L, Overgaard S, Pedersen AB, Kärrholm J, Mohaddes M, Eskelinen A, Mäkelä KT & Röhrl SM (2019) Outcome of 881 total hip arthroplasties in 747 patients 21 years or younger: data from the Nordic Arthroplasty Register Association (NARA) 1995–2016, Acta Orthopaedica, 90:4, 331-337, DOI: 10.1080/17453674.2019.1615263

Hannouche, D., Devriese, F., Delambre, J., Zadegan, F., Tourabaly, I., Sedel, L., . . . Nizard, R. (2016). Ceramic-on-ceramic THA implants in patients younger than 20 years. *Clinical Orthopaedics & Related Research, 474*(2), 520-527.

Hannouche, D., Zaoui, A., Zadegan, F., Sedel, L., & Nizard, R. (2011). Thirty years of experience with alumina-on-alumina bearings in total hip arthroplasty. *International Orthopaedics, 35*(2), 207-213. doi:10.1007/s00264-010-1187-1

Hargreaves, E. R. (1958). A survey of rheumatoid arthritis in west cornwall. *Annals of the Rheumatic Diseases, 17*(1), 61-75. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1007012/

Harmsen, R. T. E., Nicolai, M. P. J., Den Oudsten, B. L., Putter, H., Haanstra, T. M., Nolte, P. A., . . . Elzevier, H. (2017). Patient sexual function and hip replacement surgery: A survey of surgeon attitudes. *International Orthopaedics, 41*(12), 2433-2445. doi:10.1007/s00264-017-3473-7

Harmsen, R. T. E., Haanstra, T. M., Sierevelt, I. N., Jansma, E. P., Nolte, P. A., Nicolai, M. P. J., . . . Van Royen, B. J. (2016). Does total hip replacement affect sexual quality of life? *BMC Musculoskeletal Disorders, 17*, 198.

Harris, W. H. (1994). Osteolysis and particle disease in hip replacement: A review. *Acta Orthopaedica Scandinavica, 65*(1), 113-123. doi:10.3109/17453679408993734

Harris, W. H., & Sledge, C. B. (1990). Total hip and total knee replacement. *N Engl J Med, 323*(11), 725-731. doi:10.1056/NEJM199009133231106

Hartmann, A., Hannemann, F., Lützner, J., Seidler, A., Drexler, H., Günther, K., & Schmitt, J. (2013). Metal ion concentrations in body fluids after implantation of hip replacements with metal-on-metal bearing--systematic review of clinical and epidemiological studies. *PloS One, 8*(8), e70359. doi:10.1371/journal.pone.0070359

Hasegawa, M., Naito, Y., Yamaguchi, T., Miyazaki, S., Wakabayashi, H., & Sudo, A. (2016). Factors associated with symptomatic pseudotumors following metal-on-metal total hip arthroplasty. *BMC Musculoskeletal Disorders, 17*(1), 456. doi:10.1186/s12891-016-1317-z

Heikinheimo, O., Gissler, M., & Suhonen, S. (2008). Age, parity, history of abortion and contraceptive choices affect the risk of repeat abortion. *Contraception, 78*(2), 149-154. doi://dx.doi.org/10.1016/j.contraception.2008.03.013

Heikinheimo, O., Gissler, M., & Suhonen, S. (2009). Can the outcome of the next pregnancy be predicted at the time of induced abortion?. *Human Reproduction, 24*(4), 820-826. doi://dx.doi.org/10.1093/humrep/den465

Heino, A., Niinimäki, M., Mentula, M., & Gissler, M. (2018). How reliable are health registers? registration of induced abortions and sterilizations in finland. *Informatics for Health & Social Care, 43*(3), 310-319. doi:10.1080/17538157.2017.1297306

Hernigou, P. (2014). Smith–Petersen and early development of hip arthroplasty. *International Orthopaedics, 38*(1), 193. doi:10.1007/s00264-013-2080-5

Hjorth, M. H., Mechlenburg, I., Soballe, K., Roemer, L., Jakobsen, S. S., & Stilling, M. (2018). Higher prevalence of mixed or solid pseudotumors in metal-on-polyethylene total hip arthroplasty compared with metal-on-metal total hip arthroplasty and resurfacing hip arthroplasty. *The Journal of Arthroplasty, 33*(7), 2279-2286. doi:10.1016/j.arth.2018.02.011

Hognert, H., Skjeldestad, F. E., Gemzell-Danielsson, K., Heikinheimo, O., Milsom, I., Lidegaard, Ø, & Lindh, I. (2017). High birth rates despite easy access to contraception and abortion: A cross-sectional study. *Acta Obstetricia Et Gynecologica Scandinavica, 96*(12), 1414-1422. doi:10.1111/aogs.13232

Holmberg-Marttila D, Sievänen H, Tuimala R. Changes in bone mineral density during pregnancy and postpartum: prospective data on five women. *Osteoporos Int.* 1999;10(1):41-6. doi: 10.1007/s001980050192

Hunt, L. P., Blom, A. W., Matharu, G. S., Porter, M. L., & Whitehouse, M. R. (2018). The risk of developing cancer following metal-on-metal hip replacement compared with non metal-on-metal hip bearings: Findings from a prospective national registry "the national joint registry of england, wales, northern ireland and the isle of man". *PloS One, 13*(9), e0204356. doi:10.1371/journal.pone.0204356

Issa, K., Pierce, T. P., Brothers, A., Festa, A., Scillia, A. J., & Mont, M. A. (2017). Sexual activity after total hip arthroplasty: A systematic review of the outcomes. *The Journal of Arthroplasty, 32*(1), 336-340. doi:10.1016/j.arth.2016.07.052

J.F Skomsvoll, V Baste, M Østensen, L.M Irgens. (1999). Perinatal outcome in pregnancies of women with connective tissue disease and inflammatory rheumatic disease in norway. *Scandinavian Journal of Rheumatology, 28*(6), 352-356. doi:10.1080/03009749950155337

Jämsen, E., Peltola, M., Eskelinen, A., & Lehto, M. U. K. (2013). Comorbid diseases as predictors of survival of primary total hip and knee replacements: A nationwide register-based study of 96 754 operations on patients with primary osteoarthritis. *Annals of the Rheumatic Diseases, 72*(12), 1975-1982. doi:10.1136/annrheumdis-2012-202064

Jassim, S. S., Douglas, S. L., & Haddad, F. S. (2014). Athletic activity after lower limb arthroplasty: A systematic review of current evidence. *The Bone & Joint Journal, 96-B*(7), 923-927. doi:10.1302/0301-620X.96B7.31585

Jasty, M., Bragdon, C., Jiranek, W., Chandler, H., Maloney, W., & Harris, W. H. (1994). Etiology of osteolysis around porous-coated cementless total hip arthroplasties. *Clinical Orthopaedics and Related Research,* (308), 111-126.

Jensen, T. K., Andersson, A., Jørgensen, N., Andersen, A., Carlsen, E., Petersen, J. H., & Skakkebaek, N. E. (2004). Body mass index in relation to semen quality and reproductive hormones among 1,558 danish men. *Fertility and Sterility, 82*(4), 863-870. doi:10.1016/j.fertnstert.2004.03.056

Johanson, P., Furnes, O., Ivar Havelin, L., Fenstad, A. M., Pedersen, A. B., Overgaard, S., . . . Kärrholm, J. (2017). Outcome in design-specific comparisons between highly crosslinked and conventional polyethylene in total hip arthroplasty. *Acta Orthopaedica, 88*(4), 363-369. doi:10.1080/17453674.2017.1307676

Johnson, A. J., Woon, R. P., Le Duff, M. J., & Amstutz, H. C. (2013). Childhood development after maternal metal-on-metal hip resurfacing. *Hip International: The Journal of Clinical and Experimental Research on Hip Pathology and Therapy, 23*(2), 181-186. doi:10.5301/HIP.2013.10731

Jones, R. K., Darroch, J. E., & Henshaw, S. K. (2002). Patterns in the socioeconomic characteristics of women obtaining abortions in 2000-2001. *Perspectives on Sexual and Reproductive Health, 34*(5), 226-235.

Junaid, M., Murthy, R. C., & Saxena, D. K. (1995). Chromium fetotoxicity in mice during late pregnancy. *Veterinary and Human Toxicology, 37*(4), 320-323.

K Huch, K A C Muller, T Sturmer, H Brenner, W Puhl, & K-P Gunther. (2006). Sports activities 5 years after total knee or hip arthroplasty: The ulm osteoarthritis study. *British Journal of Sports Medicine, 40*(2), 113. Retrieved from https://search.proquest.com/docview/1779008882

Källén, B., Rydhstroem, H., & Aberg, A. (2000). Asthma during pregnancy--a population based study. *European Journal of Epidemiology, 16*(2), 167-171.

Kanojia, R. K., Junaid, M., & Murthy, R. C. (1998). Embryo and fetotoxicity of hexavalent chromium: A long-term study. *Toxicology Letters, 95*(3), 165-172.

Kasten, U., Mullenders, L. H., & Hartwig, A. (1997). Cobalt(II) inhibits the incision and the polymerization step of nucleotide excision repair in human fibroblasts. *Mutation Research, 383*(1), 81-89.

Katz, P. P. (2006). Childbearing decisions and family size among women with rheumatoid arthritis. *Arthritis Care & Research, 55*(2), 217-223. doi:10.1002/art.21859

Kearns, S. R., Jamal, B., Rorabeck, C. H., & Bourne, R. B. (2006). Factors affecting survival of uncemented total hip arthroplasty in patients 50 years or younger. *Clinical Orthopaedics and Related Research, 453*, 103-109. doi:10.1097/01.blo.0000238868.22852.dd

Keegan, G. M., Learmonth, I. D., & Case, C. P. (2008). A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. *Critical Reviews in Toxicology, 38*(8), 645-674. doi:10.1080/10408440701845534

Kela. (2018). Erityiskorvattavuus - reimbursements, kela. Retrieved from https://www.kela.fi/laakkeet_erityiskorvaus

Kersten, I., Lange, A. E., Haas, J. P., Fusch, C., Lode, H., Hoffmann, W., & Thyrian, J. R. (2014). Chronic diseases in pregnant women: Prevalence and birth outcomes based on the SNiP-study. *BMC Pregnancy and Childbirth, 14*, 75. doi:10.1186/1471-2393-14-75

Kjaer, K., Hagen, C., Sandø, S. H., & Eshøj, O. (1992). Infertility and pregnancy outcome in an unselected group of women with insulin-dependent diabetes mellitus. *American Journal of Obstetrics and Gynecology, 166*(5), 1412-1418. doi:10.1016/0002-9378(92)91613-F

Klit, J., Jacobsen, S., Schmiegelow, V., Sonne-Holm, S., & Troelsen, A. (2015). Alternative outcome measures in young total hip arthroplasty patients: A prospective cohort study. *Hip International: The Journal of Clinical and Experimental Research on Hip Pathology and Therapy, 25*(2), 152-159. doi:10.5301/hipint.5000200

Knight, S. R., Aujla, R., & Biswas, S. P. (2011). Total hip arthroplasty - over 100 years of operative history. *Orthopedic Reviews, 3*(2) doi:10.4081/or.2011.e16

Korovessis, P., Petsinis, G., Repanti, M., & Repantis, T. (2006). Metallosis after contemporary metal-on-metal total hip arthroplasty. five to nine-year follow-up. *The Journal of Bone and Joint Surgery. American Volume, 88*(6), 1183-1191. doi:10.2106/JBJS.D.02916

Kort, H. I., Massey, J. B., Elsner, C. W., Mitchell-Leef, D., Shapiro, D. B., Witt, M. A., & Roudebush, W. E. (2006). Impact of body mass index values on sperm quantity and quality. *Journal of Andrology, 27*(3), 450-452. doi:10.2164/jandrol.05124

Kovac, J. R., Khanna, A., & Lipshultz, L. I. (2015). The effects of cigarette smoking on male fertility. *Postgraduate Medicine, 127*(3), 338-341. doi:10.1080/00325481.2015.1015928

Kovacs, C.S. Osteoporosis presenting in pregnancy, puerperium, and lactation. (2014) *Curr Opin Endocrinol Diabetes Obes.* 2014 Dec;21(6):468-75. doi: 10.1097/MED.0000000000000102.

Kurtz, S. M., Lau, E., Ong, K., Zhao, K., Kelly, M., & Bozic, K. J. (2009). Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. *Clinical Orthopaedics and Related Research, 467*(10), 2606-2612. doi:10.1007/s11999-009-0834-6

Laanpere, M., Ringmets, I., Part, K., Allvee, K., Veerus, P., & Karro, H. (2014). Abortion trends from 1996 to 2011 in estonia: Special emphasis on repeat abortion. *BMC Women's Health, 14*, 81.

Laffosse, J., Tricoire, J., Chiron, P., & Puget, J. (2008). Sexual function before and after primary total hip arthroplasty. *Joint, Bone, Spine: Revue Du Rhumatisme, 75*(2), 189-194. doi:10.1016/j.jbspin.2007.05.006

Lainiala, O., Elo, P., Reito, A., Pajamäki, J., Puolakka, T., & Eskelinen, A. (2014). Comparison of extracapsular pseudotumors seen in magnetic resonance imaging and in revision surgery of 167 failed metal-on-metal hip replacements. *Acta Orthopaedica, 85*(5), 474-479. doi:10.3109/17453674.2014.934189

Lainiala, O., Elo, P., Reito, A., Pajamäki, J., Puolakka, T., & Eskelinen, A. (2015). Good sensitivity and specificity of ultrasound for detecting pseudotumors in 83 failed metal-on-metal hip replacements. *Acta Orthopaedica, 86*(3), 339-344. doi:10.3109/17453674.2014.1001970

Lainiala, O., Reito, A., Elo, P., Pajamäki, J., Puolakka, T., & Eskelinen, A. (2015). Revision of metal-on-metal hip prostheses results in marked reduction of blood cobalt and chromium ion concentrations. *Clinical Orthopaedics and Related Research, 473*(7), 2305-2313. doi:10.1007/s11999-015-4156-6

Lally, L., Mandl, L. A., Huang, W., & Goodman, S. M. (2015). Pregnancy does not adversely affect postoperative pain and function in women with total hip arthroplasty. *JCR: Journal of Clinical Rheumatology, 21*(6), 323-325.

Langen, E. S., Chakravarty, E. F., Liaquat, M., El-Sayed, Y. Y., & Druzin, M. L. (2014). High rate of preterm birth in pregnancies complicated by rheumatoid arthritis. *American Journal of Perinatology, 31*(1), 9-14. doi:10.1055/s-0033-1333666

Langton, D. J., Jameson, S. S., Joyce, T. J., Gandhi, J. N., Sidaginamale, R., Mereddy, P., . . . Nargol, A. V. F. (2011). Accelerating failure rate of the ASR total hip replacement. *The Journal of Bone and Joint Surgery. British Volume, 93*(8), 1011-1016. doi:10.1302/0301-620X.93B8.26040

Langton, D. J., Jameson, S. S., Joyce, T. J., Hallab, N. J., Natu, S., & Nargol, A. V. F. (2010). Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. *The Journal of Bone and Joint Surgery. British Volume, 92*(1), 38-46. doi:10.1302/0301-620X.92B1.22770

Langton, D. J., Joyce, T. J., Jameson, S. S., Lord, J., Van Orsouw, M., Holland, J. P., . . . De Smet, K. A. (2011). Adverse reaction to metal debris following hip resurfacing: The influence of component type, orientation and volumetric wear. *The Journal of Bone and Joint Surgery. British Volume, 93*(2), 164-171. doi:10.1302/0301-620X.93B2.25099

Lapolla, A., Dalfrà, M. G., Di Cianni, G., Bonomo, M., Parretti, E., & Mello, G. (2008). A multicenter italian study on pregnancy outcome in women with diabetes. *Nutrition, Metabolism and Cardiovascular Diseases, 18*(4), 291-297. doi:10.1016/j.numecd.2006.12.001

Lari Lehtovirta, Aleksi Reito, Jyrki Parkkinen, Sirpa Peräniemi, Jouko Vepsäläinen, & Antti Eskelinen. (2018). Association between periprosthetic tissue metal content, whole blood and synovial fluid metal ion levels and histopathological findings in patients with failed metal-on-metal hip replacement. *PLoS One, 13*(5), e0197614. doi:10.1371/journal.pone.0197614

Lauenborg, J., Mathiesen, E., Ovesen, P., Westergaard, J. G., Ekbom, P., Mølsted-Pedersen, L., & Damm, P. (2003). Audit on stillbirths in women with pregestational type 1 diabetes. *Diabetes Care, 26*(5), 1385-1389.

Learmonth, I. D., Young, C., & Rorabeck, C. (2007). The operation of the century: Total hip replacement. *Lancet (London, England), 370*(9597), 1508-1519. doi:10.1016/S0140-6736(07)60457-7

Lehtovirta, L., Reito, A., Lainiala, O., Parkkinen, J., Hothi, H., Henckel, J., . . . Eskelinen, A. (2019). Host-specific factors affect the pathogenesis of adverse reaction to metal debris. *BMC Musculoskeletal Disorders, 20* doi:10.1186/s12891-019-2578-0

Lehtovirta, L., Reito, A., Parkkinen, J., Hothi, H., Henckel, J., Hart, A., & Eskelinen, A. (2017). Analysis of bearing wear, whole blood and synovial fluid metal ion concentrations and histopathological findings in patients with failed ASR hip resurfacings. *BMC Musculoskeletal Disorders, 18* doi:10.1186/s12891-017-1894-5

Leipälä, J., Ignatius, J., Autti-Rämö, I., & Mäkelä, M. (2009). *Sikiöseulonnat: Opas raskaana oleville : Tietoa sikiön kromosomi- ja rakennepoikkeavuuksien seulonnoista*. http://www.julkari.fi/handle/10024/80233: Terveyden ja hyvinvoinnin laitos (THL). Retrieved from http://www.julkari.fi/handle/10024/80233

Leppälahti, S., Gissler, M., Mentula, M., & Heikinheimo, O. (2012). Trends in teenage termination of pregnancy and its risk factors: A population-based study in finland, 1987-2009. *Human Reproduction (Oxford, England), 27*(9), 2829-2836. doi:10.1093/humrep/des253

Lie, S. A., Engesaeter, L. B., Havelin, L. I., Gjessing, H. K., & Vollset, S. E. (2004). Dependency issues in survival analyses of 55,782 primary hip replacements from 47,355 patients. *Statistics in Medicine, 23*(20), 3227-3240. doi:10.1002/sim.1905

Lin, Y., Chen, K., Peng, Y., Chen, P., & Yang, Y. (2018). Type 1 diabetes impairs female fertility even before it is diagnosed. *Diabetes Research and Clinical Practice, 143*, 151-158. doi:10.1016/j.diabres.2018.07.010

Lombardi, A. V., Skeels, M. D., Berend, K. R., Adams, J. B., & Franchi, O. J. (2011). Do large heads enhance stability and restore native anatomy in primary total hip arthroplasty? *Clinical Orthopaedics and Related Research, 469*(6), 1547-1553. doi:10.1007/s11999-010-1605-0

López-López, J. A., Humphriss, R. L., Beswick, A. D., Thom, H. H. Z., Hunt, L. P., Burston, A., . . . Marques, E. M. R. (2017). Choice of implant combinations in total hip replacement: Systematic review and network meta-analysis. *BMJ (Clinical Research Ed.), 359*, j4651. doi:10.1136/bmj.j4651

Lorenzen, T., Pociot, F., Johannesen, J., Kristiansen, O. P., & Nerup, J. (1999). A population-based survey of frequencies of self-reported spontaneous and induced abortions in danish women with type 1 diabetes mellitus. danish IDDM epidemiology and genetics group. *Diabetic Medicine: A Journal of the British Diabetic Association, 16*(6), 472-476.

Lübbeke, A., Zimmermann-Sloutskis, D., Stern, R., Roussos, C., Bonvin, A., Perneger, T., . . . Hoffmeyer, P. (2014). Physical activity before and after primary total hip arthroplasty: A registry-based study. *Arthritis Care & Research, 66*(2), 277-284. doi:10.1002/acr.22101

Macintosh, M. C. M., Fleming, K. M., Bailey, J. A., Doyle, P., Modder, J., Acolet, D., . . . Miller, A. (2006). Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in england, wales, and northern ireland: Population based study. *BMJ (Clinical Research Ed.), 333*(7560), 177. doi:10.1136/bmj.38856.692986.AE

Maffulli, N., Del Buono, A., & Denaro, V. (2012). Hip artroplasty: A transient reason not to be pregnant. *Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland, 10*(6), 347-349. doi://dx.doi.org/10.1016/j.surge.2011.10.004

Makarewich, C. A., Anderson, M. B., Gililland, J. M., Pelt, C. E., & Peters, C. L. (2018). Ten-year survivorship of primary total hip arthroplasty in patients 30 years of age or younger. *The Bone & Joint Journal, 100-B*(7), 867-874. doi:10.1302/0301-620X.100B7.BJJ-2017-1603.R1

Mäkelä, K. T., Visuri, T., Pulkkinen, P., Eskelinen, A., Remes, V., Virolainen, P., . . . Pukkala, E. (2012). Risk of cancer with metal-on-metal hip replacements: Population based study. *BMJ (Clinical Research Ed.), 345*, e4646. doi:10.1136/bmj.e4646

Mäkelä, K. T., Visuri, T., Pulkkinen, P., Eskelinen, A., Remes, V., Virolainen, P., . . . Pukkala, E. (2014a). Cancer incidence and cause-specific mortality in patients with metal-on-metal hip replacements in finland. *Acta Orthopaedica, 85*(1), 32-38. doi:10.3109/17453674.2013.878830

Mäkelä, K. T., Matilainen, M., Pulkkinen, P., Fenstad, A. M., Havelin, L. I., Engesaeter, L., . . . Eskelinen, A. (2014b). Countrywise results of total hip replacement. *Acta Orthopaedica, 85*(2), 107-116. doi:10.3109/17453674.2014.893498

Malm, H., Artama, M., Gissler, M., & Ritvanen, A. (2011). Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstetrics and Gynecology, 118*(1), 111-120. doi:10.1097/AOG.0b013e318220edcc

Maradit Kremers, H., Larson, D. R., Crowson, C. S., Kremers, W. K., Washington, R. E., Steiner, C. A., . . . Berry, D. J. (2015). Prevalence of total hip and knee replacement in the united states. *The Journal of Bone and Joint Surgery. American Volume, 97*(17), 1386-1397. doi:10.2106/JBJS.N.01141

Marchi, J., Berg, M., Dencker, A., Olander, E. K., & Begley, C. (2015). Risks associated with obesity in pregnancy, for the mother and baby: A systematic review of reviews. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity, 16*(8), 621-638. doi:10.1111/obr.12288

Marques, E. M. R., Humphriss, R., Welton, N. J., Higgins, J. P. T., Hollingworth, W., Lopez-Lopez, J. A., . . . Beswick, A. D. (2016). The choice between hip prosthetic bearing surfaces in total hip replacement: A protocol for a systematic review and network meta-analysis. *Systematic Reviews, 5* doi:10.1186/s13643-016-0189-5

Martini, A. C., Tissera, A., Estofán, D., Molina, R. I., Mangeaud, A., de Cuneo, M. F., & Ruiz, R. D. (2010). Overweight and seminal quality: A study of 794 patients. *Fertility and Sterility, 94*(5), 1739-1743. doi:10.1016/j.fertnstert.2009.11.017

Massin, P., & Achour, S. (2017). Wear products of total hip arthroplasty: The case of polyethylene. *Morphologie: Bulletin De L'Association Des Anatomistes, 101*(332), 1-8. doi:10.1016/j.morpho.2016.06.001

Mathiesen, E. R., Ringholm, L., & Damm, P. (2011). Stillbirth in diabetic pregnancies. *Best Practice & Research. Clinical Obstetrics & Gynaecology, 25*(1), 105-111. doi:10.1016/j.bpobgyn.2010.11.001

McDonald, S. D., Han, Z., Mulla, S., & Beyene, J. (2010). Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: Systematic review and meta-analyses. *BMJ (Clinical Research Ed.), 341*, c3428. doi:10.1136/bmj.c3428

McDowell, C., & Lachiewicz, P. (2001). Pregnancy after total hip arthroplasty. *J Bone Joint Surg Am, 83*(10), 1490-1494.

McFadden, B. (2013). Is there a safe coital position after a total hip arthroplasty? *Orthopedic Nursing, 32*(4), 228. doi:10.1097/NOR.0b013e31829b0349

McKee, G. K., & Watson-Farrar, J. (1966). Replacement of arthritic hips by the McKee-farrar prosthesis. *The Journal of Bone and Joint Surgery. British Volume, 48*(2), 245-259.

McKellop, H. A., Campbell, P., Park, S. H., Schmalzried, T. P., Grigoris, P., Amstutz, H. C., & Sarmiento, A. (1995). The origin of submicron polyethylene wear debris in total hip arthroplasty. *Clinical Orthopaedics and Related Research,* (311), 3-20.

McMinn, D. J. W. (2003). Development of metal/metal hip resurfacing. *Hip International: The Journal of Clinical and Experimental Research on Hip Pathology and Therapy, 13*(1), 41-53. doi:10.5301/HIP.2013.11462

Medenica, S., Nedeljkovic, O., Radojevic, N., Stojkovic, M., Trbojevic, B., & Pajovic, B. (2015). Thyroid dysfunction and thyroid autoimmunity in euthyroid women in achieving fertility. *European Review for Medical and Pharmacological Sciences, 19*(6), 977-987.

Meldrum, R., Feinberg, J., Capello, W., & Detterline, A. (2003). Clinical outcome and incidence of pregnancy after bipolar and total hip arthroplasty in young women. *J Arthroplasty, 18*(7), 879-885.

Mellon, S. J., Liddle, A. D., & Pandit, H. (2013). Hip replacement: Landmark surgery in modern medical history. *Maturitas, 75*(3), 221-226. doi:10.1016/j.maturitas.2013.04.011

MHRA. (2010). *Medical device alert - all MoM hip replacements * ().Medicines and Healthcare products Regulatory Agency.

Miyamoto T, Miyakoshi K, Sato Y, Kasuga Y, Ikenoue S, Miyamoto K, Nishiwaki Y, Tanaka M, Nakamura M, Matsumoto M. Changes in bone metabolic profile associated with pregnancy or lactation. *Sci Rep.* 2019 May 13;9(1):6787. doi: 10.1038/s41598-019-43049-1.

Miettinen, A. (2015). *Suomalaisten lastensaantiin liittyviä toiveita ja odotuksia -perhebarometri 2015 - väestöliitto.* (). www.vaestoliitto.fi: Väestöliitto. Retrieved from www.vaetoliitto.fi

Migaud, H., Putman, S., Kern, G., Isida, R., Girard, J., Ramdane, N., . . . Hamadouche, M. (2016). Do the reasons for ceramic-on-ceramic revisions differ from other bearings in total hip arthroplasty? *Clinical Orthopaedics and Related Research, 474*(10), 2190-2199. doi:10.1007/s11999-016-4917-x

Mintziori, G., Kita, M., Duntas, L., & Goulis, D. G. (2016). Consequences of hyperthyroidism in male and female fertility: Pathophysiology and current management. *Journal of Endocrinological Investigation, 39*(8), 849-853. doi:10.1007/s40618-016-0452-6

Monaghan, J., Lenehan, P., Stronge, J., & Gallagher, J. (1987). Pregnancy and vaginal delivery following bilateral total hip replacement. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 26*(3), 261-264.

Münger, P., Röder, C., Ackermann-Liebrich, U., & Busato, A. (2006). Patient-related risk factors leading to aseptic stem loosening in total hip arthroplasty: A case-control study of 5,035 patients. *Acta Orthopaedica, 77*(4), 567-574. doi:10.1080/17453670610012629

Murphy, V. E., Wang, G., Namazy, J. A., Powell, H., Gibson, P. G., Chambers, C., & Schatz, M. (2013). The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: A systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics and Gynaecology, 120*(7), 812-822. doi:10.1111/1471-0528.12224

Murphy, V. E., Jensen, M. E., & Gibson, P. G. (2017). Asthma during pregnancy: Exacerbations, management, and health outcomes for mother and infant. *Seminars in Respiratory and Critical Care Medicine, 38*(2), 160-173. doi:10.1055/s-0037-1600906

Nasri, H. Z., Houde Ng, K., Westgate, M., Hunt, A., & Holmes, L. B. (2018). Malformations among infants of mothers with insulin-dependent diabetes: Is there a recognizable pattern of abnormalities? *Birth Defects Research, 110*(2), 108-113. doi:10.1002/bdr2.1155

Natu, S., Sidaginamale, R. P., Gandhi, J., Langton, D. J., & Nargol, A. V. F. (2012). Adverse reactions to metal debris: Histopathological features of periprosthetic soft tissue reactions seen in association with failed metal on metal hip arthroplasties. *Journal of Clinical Pathology, 65*(5), 409-418. doi:10.1136/jclinpath-2011-200398

Nelson, J. L., & Ostensen, M. (1997). Pregnancy and rheumatoid arthritis. *Rheumatic Diseases Clinics of North America, 23*(1), 195-212.

Nisén, J., Myrskylä, M., Silventoinen, K., & Martikainen, P. (2014). Effect of family background on the educational gradient in lifetime fertility of finnish women born 1940–50. *Population Studies, 68*(3), 321-337. doi:10.1080/00324728.2014.913807

NJR. (2018). *15th annual report of the national joint registry.* (). Retrieved from http://www.njrreports.org.uk/Portals/0/PDFdownloads/NJR%2015th%20Annual%20Report%202018.pdf

Noordin, S., & Masri, B. (2012). Periprosthetic osteolysis: Genetics, mechanisms and potential therapeutic interventions. *Canadian Journal of Surgery. Journal Canadien De Chirurgie, 55*(6), 408-417. doi:10.1503/cjs.003711

Nørgaard, M., Larsson, H., Pedersen, L., Granath, F., Askling, J., Kieler, H., . . . Stephansson, O. (2010). Rheumatoid arthritis and birth outcomes: A danish and swedish nationwide prevalence study. *Journal of Internal Medicine, 268*(4), 329-337. doi:10.1111/j.1365-2796.2010.02239.x

Novak, C. C., Hsu, A. R., Della Valle, C. J., Skipor, A. K., Campbell, P., Amstutz, H. C., . . . Jacobs, J. J. (2014). Metal ion levels in maternal and placental blood after metal-on-metal total hip arthroplasty. *American Journal of Orthopedics (Chatham, Nj), 43*(12), 304.

Nunley, R. M., Nam, D., Bashyal, R. K., Della Valle, C. J., Hamilton, W. G., Berend, M. E., . . . Barrack, R. L. (2015). The impact of total joint arthroplasty on sexual function in young, active patients. *The Journal of Arthroplasty, 30*(2), 335-340. doi:10.1016/j.arth.2014.09.029

Oboni, J., Marques-Vidal, P., Bastardot, F., Vollenweider, P., & Waeber, G. (2016). Impact of smoking on fertility and age of menopause: A population-based assessment. *BMJ Open, 6*(11), e012015. doi:10.1136/bmjopen-2016-012015

Ollivere, B., Darrah, C., Barker, T., Nolan, J., & Porteous, M. J. (2009). Early clinical failure of the birmingham metal-on-metal hip resurfacing is associated with metallosis and soft-tissue necrosis. *The Journal of Bone and Joint Surgery. British Volume, 91*(8), 1025-1030. doi:10.1302/0301-620X.91B8.21701

Oppermann, M., Borisch, C., & Schaefer, C. (2015). Hip arthroplasty with high chromium and cobalt blood levels--case report of a patient followed during pregnancy and lactation period. *Reproductive Toxicology (Elmsford, N.Y.), 53*, 51-53. doi:10.1016/j.reprotox.2015.03.009

Ostensen, M. (1993). [Hip prostheses in women of fertile age. consequences for sexuality and reproduction]. [Hofteproteser hos kvinner i fertil alder. Konsekvenser for seksualitet og reproduksjon.] *Tidsskrift for Den Norske Laegeforening, 113*(12), 1483-1485.

Øyen, N., Diaz, L. J., Leirgul, E., Boyd, H. A., Priest, J., Mathiesen, E. R., . . . Melbye, M. (2016). Prepregnancy diabetes and offspring risk of congenital heart disease: A nationwide cohort study. *Circulation, 133*(23), 2243-2253. doi:10.1161/CIRCULATIONAHA.115.017465

Park, Y., Moon, Y., Lim, S., Yang, J., Ahn, G., & Choi, Y. (2005a). Early osteolysis following second-generation metal-on-metal hip replacement. *The Journal of Bone and Joint Surgery. American Volume, 87*(7), 1515-1521. doi:10.2106/JBJS.D.02641

Park, Y., Moon, Y., Lim, S., Yang, J., Ahn, G., & Choi, Y. (2005b). Early osteolysis following second-generation metal-on-metal hip replacement. *The Journal of Bone and Joint Surgery. American Volume, 87*(7), 1515-1521. doi:10.2106/JBJS.D.02641

Patel, N. K., Luff, T., Whittingham-Jones, P., Gooding, C. R., & Hashemi-Nejad, A. (2012). Total hip arthroplasty in teenagers: An alternative to hip arthrodesis. *Hip International: The Journal of Clinical and Experimental Research on Hip Pathology and Therapy, 22*(6), 621-627. doi:10.5301/HIP.2012.10352

Pedersen, A. B., Mehnert, F., Havelin, L. I., Furnes, O., Herberts, P., Kärrholm, J., . . . Overgaard, S. (2014). Association between fixation technique and revision risk in total hip arthroplasty patients younger than 55 years of age. results from the nordic arthroplasty register association. *Osteoarthritis and Cartilage, 22*(5), 659-667. doi:10.1016/j.joca.2014.03.005

Pennell, P. B., French, J. A., Harden, C. L., Davis, A., Bagiella, E., Andreopoulos, E., . . . Allien, S. (2018). Fertility and birth outcomes in women with epilepsy seeking pregnancy. *JAMA Neurology, 75*(8), 962-969. doi:10.1001/jamaneurol.2018.0646

Perez, G., Garcia-Subirats, I., Rodriguez-Sanz, M., Diez, E., & Borrell, C. (2010). Trends in inequalities in induced abortion according to educational level among urban women. *Journal of Urban Health, 87*(3), 524-530.

Perez, G., Ruiz-Munoz, D., Gotsens, M., Cases, M. C., & Rodriguez-Sanz, M. (2014). Social and economic inequalities in induced abortion in spain as a function of individual and contextual factors. *European Journal of Public Health, 24*(1), 162-169.

Pohjoranta, E., Mentula, M., Gissler, M., Suhonen, S., & Heikinheimo, O. (2015). Provision of intrauterine contraception in association with first trimester induced abortion reduces the need of repeat abortion: First-year results of a randomized controlled trial. *Human Reproduction, 30*(11), 2539-2546. doi:10.1093/humrep/dev233

Population Register Centre. (2019). Population information system - väestötietojärjestelmä. Retrieved from https://vrk.fi/en/population-information-system

Puolakka TJS, Pajamäki J, Halonen PJ, Pulkkinen PO, Paavolainen P, Nevalainen JK. (2001). The Finnish Arthroplasty Register, Report of the hip register. *Acta Orthop Scand* 2001; 72 (5): 433–441

Posfai, E., Banhidy, F., Urban, R., & Czeizel, A. E. (2015). Birth outcomes of children born to women with rheumatoid arthritis. *Central European Journal of Public Health, 23*(2), 104-110.

Rankin, J., Tennant, P. W. G., Stothard, K. J., Bythell, M., Summerbell, C. D., & Bell, R. (2010). Maternal body mass index and congenital anomaly risk: A cohort study. *International Journal of Obesity (2005), 34*(9), 1371-1380. doi:10.1038/ijo.2010.66

Ranstam, J., & Robertsson, O. (2010). Statistical analysis of arthroplasty register data. *Acta Orthopaedica, 81*(1), 10-14. doi:10.3109/17453671003587168

Rasanen, P., Paavolainen, P., Sintonen, H., Koivisto, A. M., Blom, M., & Ryynanen, O. P. (2007). Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. *Acta Orthopediatrica, 78*(1), 108-115.

Rasch, V., Gammeltoft, T., Knudsen, L. B., Tobiassen, C., Ginzel, A., & Kempf, L. (2008). Induced abortion in denmark: Effect of socio-economic situation and country of birth. *European Journal of Public Health, 18*(2), 144-149. doi:10.1093/eurpub/ckm112

Raskaudenkeskeytykset - THL. (2018). Retrieved from http://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/raskaudenkeskeytykset/raskaudenkeskeytykset

Razaz, N., Tomson, T., Wikström, A., & Cnattingius, S. (2017). Association between pregnancy and perinatal outcomes among women with epilepsy. *JAMA Neurology, 74*(8), 983-991. doi:10.1001/jamaneurol.2017.1310

Reckling, F. W. (1976). Normal pregnancy and delivery following total hip joint replacement. *Clinical Orthopaedics and Related Research,* (115), 169-171.

Regushevskaya, E., Dubikaytis, T., Laanpere, M., Nikula, M., Kuznetsova, O., Haavio-Mannila, E., . . . Hemminki, E. (2009). Risk factors for induced abortions in st petersburg, estonia and finland. results from surveys among women of reproductive age. *The European Journal of Contraception & Reproductive Health Care: The Official Journal of the European Society of Contraception, 14*(3), 176-186. doi:10.1080/13625180902916038

Reiss, K., Breckenkamp, J., Borde, T., Brenne, S., Henrich, W., David, M., & Razum, O. (2016). The association of pre-pregnancy overweight and obesity with delivery outcomes: A comparison of immigrant and non-immigrant women in berlin, germany. *International Journal of Public Health, 61*(4), 455-463. doi:10.1007/s00038-016-0825-9

Reito, A., Puolakka, T., Elo, P., Pajamäki, J., & Eskelinen, A. (2013). High prevalence of adverse reactions to metal debris in small-headed ASR™ hips. *Clinical Orthopaedics and Related Research, 471*(9), 2954-2961. doi:10.1007/s11999-013-3023-6

Rejnö, G., Lundholm, C., Gong, T., Larsson, K., Saltvedt, S., & Almqvist, C. (2014). Asthma during pregnancy in a population-based study--pregnancy complications and adverse perinatal outcomes. *PloS One, 9*(8), e104755. doi:10.1371/journal.pone.0104755

Rissanen, P., Aro, S., Slatis, P., Sintonen, H., & Paavolainen, P. (1995). Health and quality of life before and after hip or knee arthroplasty. *Journal of Arthroplasty, 10*(2), 169-175.

Ritter, M. A., & Meding, J. B. (1987). Total hip arthroplasty. can the patient play sports again? *Orthopedics, 10*(10), 1447-1452.

Saari, A., Sankilampi, U., Hannila, M., Kiviniemi, V., Kesseli, K., & Dunkel, L. (2011). New finnish growth references for children and adolescents aged 0 to

20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. *Annals of Medicine, 43*(3), 235-248.
Salo, H., Tekay, A., & Mäkikallio, K. (2015). Tutkimusnäyttöön perustuva keisarileikkaus. *Aikakausikirja Duodecim, 131*(12), 1137-1143.
Salo, P. P., Honkanen, P. B., Ivanova, I., Reito, A., Pajamäki, J., & Eskelinen, A. (2017). High prevalence of noise following delta ceramic-on-ceramic total hip arthroplasty. *The Bone & Joint Journal, 99-B*(1), 44-50. doi:10.1302/0301-620X.99B1.37612
Salvati, E. A., Wilson, P. D., Jolley, M. N., Vakili, F., Aglietti, P., & Brown, G. C. (1981). A ten-year follow-up study of our first one hundred consecutive charnley total hip replacements. *The Journal of Bone and Joint Surgery. American Volume, 63*(5), 753-767.
Sato, T., Sugiyama, T., Kurakata, M., Saito, M., Sugawara, J., Yaegashi, N., . . . Toyoda, N. (2014). Pregnancy outcomes in women with type 1 and type 2 diabetes mellitus in a retrospective multi-institutional study in japan. *Endocrine Journal, 61*(8), 759-764.
Sauvé, P., Mountney, J., Khan, T., De Beer, J., Higgins, B., & Grover, M. (2007). Metal ion levels after metal-on-metal ring total hip replacement: A 30-year follow-up study. *The Journal of Bone and Joint Surgery. British Volume, 89*(5), 586-590. doi:10.1302/0301-620X.89B5.18457
Schatz, M., Harden, K., Forsythe, A., Chilingar, L., Hoffman, C., Sperling, W., & Zeiger, R. S. (1988). The course of asthma during pregnancy, post partum, and with successive pregnancies: A prospective analysis. *The Journal of Allergy and Clinical Immunology, 81*(3), 509-517.
Schmalzried, T. P., Jasty, M., & Harris, W. H. (1992). Periprosthetic bone loss in total hip arthroplasty. polyethylene wear debris and the concept of the effective joint space. *The Journal of Bone and Joint Surgery. American Volume, 74*(6), 849-863.
Schmalzried, T. P., Jasty, M., Rosenberg, A., & Harris, W. H. (1994). Polyethylene wear debris and tissue reactions in knee as compared to hip replacement prostheses. *Journal of Applied Biomaterials: An Official Journal of the Society for Biomaterials, 5*(3), 185-190. doi:10.1002/jab.770050302
Scully, W. F., & Teeny, S. M. (2013). Pseudotumor associated with metal-on-polyethylene total hip arthroplasty. *Orthopedics, 36*(5), 666. doi:10.3928/01477447-20130426-33
Sedgh, G., Henshaw, S., Singh, S., Ahman, E., & Shah, I. H. (2007). Induced abortion: Estimated rates and trends worldwide. *Lancet, 370*(9595), 1338-1345. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med5&AN=17933648
http://sfx.nelliportaali.fi/nelli06b?sid=OVID&isbn=&issn=0140-6736&volume=370&issue=9595&date=2007&title=Lancet&atitle=Induced

+abortion%3A+estimated+rates+and+trends+worldwide.&aulast=Sedgh+G&spage=1338
Serrano, P. M., Rodrigues, C., S. Silva, M., Coelho, R., Cardoso, P., & Oliveira, V. (2018). Pseudotumor complicating a well-fixed ceramic-on-polyethylene total hip arthroplasty. *Clinical Case Reports, 6*(9), 1756-1760. doi:10.1002/ccr3.1720
Shahrdar, C. (2011). Pseudotumor in large-diameter metal-on-metal total hip articulation. *The Journal of Arthroplasty, 26*(4), 23. doi:10.1016/j.arth.2010.05.022
Shaked, E., Wainstock, T., Sheiner, E., & Walfisch, A. (2019). Maternal asthma: Pregnancy course and outcome. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 32*(1), 103-108. doi:10.1080/14767058.2017.1372414
SHAR. (2019). The swedish hip arthroplasty register - report 2018. *The Swedish Hip Arthroplasty Register,* Retrieved from https://shpr.registercentrum.se/shar-in-english/the-swedish-hip-arthroplasty-register/p/ryouZwaoe
Sheffield, J. S., Butler-Koster, E. L., Casey, B. M., McIntire, D. D., & Leveno, K. J. (2002). Maternal diabetes mellitus and infant malformations. *Obstetrics and Gynecology, 100*(5 Pt 1), 925-930.
Sibai, B. M., Caritis, S., Hauth, J., Lindheimer, M., VanDorsten, J. P., MacPherson, C., . . . McNellis, D. (2000). Risks of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus. national institute of child health and human development network of maternal-fetal medicine units. *American Journal of Obstetrics and Gynecology, 182*(2), 364-369.
Sibai, B. M. (2002). Chronic hypertension in pregnancy. *Obstetrics and Gynecology, 100*(2), 369-377.
Sierra, R., Trousdale, R., & Cabanela, M. (2005). Pregnancy and childbirth after total hip arthroplasty. *J Bone Joint Surg Br, 87*(1), 21-24.
Sihvonen, S., & Pertovaara, M. (2019). Reumasairaudet raskauden aikana. *Aikakausikirja Duodecim, 135*(3), 257-264.
Silvestris, E., de Pergola, G., Rosania, R., & Loverro, G. (2018). Obesity as disruptor of the female fertility. *Reproductive Biology and Endocrinology: RB&E, 16*(1), 22. doi:10.1186/s12958-018-0336-z
Singh, G., Meyer, H., Ruetschi, M., Chamaon, K., Feuerstein, B., & Lohmann, C. H. (2013). Large-diameter metal-on-metal total hip arthroplasties: A page in orthopedic history? *Journal of Biomedical Materials Research. Part A, 101*(11), 3320-3326. doi:10.1002/jbm.a.34619
Siopack, J. S., & Jergesen, H. E. (1995). Total hip arthroplasty. *The Western Journal of Medicine, 162*(3), 243-249.
Siu, S., & Colman, J. (2001). Heart disease and pregnancy. *Heart, 85*(6), 710-715. doi:10.1136/heart.85.6.710

Sjöberg, L., Pitkäniemi, J., Haapala, L., Kaaja, R., & Tuomilehto, J. (2013). Fertility in people with childhood-onset type 1 diabetes. *Diabetologia, 56*(1), 78-81. doi:10.1007/s00125-012-2731-x

Skjeldestad, F. E. (1994). The incidence of repeat induced abortion--a prospective cohort study. *Acta Obstetricia Et Gynecologica Scandinavica, 73*(9), 706-710.

Skomsvoll, J. F., Ostensen, M., Baste, V., & Irgens, L. M. (2001). Number of births, interpregnancy interval, and subsequent pregnancy rate after a diagnosis of inflammatory rheumatic disease in norwegian women. *The Journal of Rheumatology, 28*(10), 2310-2314.

Skytta, E. T., Leskinen, J., Eskelinen, A., Huhtala, H., & Remes, V. (2011). Increasing incidence of hip arthroplasty for primary osteoarthritis in 30- to 59-year-old patients. *Acta Orthopaedica, 82*(1), 1-5.

Smith, A. J., Dieppe, P., Howard, P. W., & Blom, A. W. (2012). Failure rates of metal-on-metal hip resurfacings: Analysis of data from the national joint registry for england and wales. *Lancet (London, England), 380*(9855), 1759-1766. doi:10.1016/S0140-6736(12)60989-1

Smith, A. J., Dieppe, P., Porter, M., & Blom, A. W. (2012). Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: Linkage study between the national joint registry of england and wales and hospital episode statistics. *BMJ (Clinical Research Ed.), 344*, e2383. doi:10.1136/bmj.e2383

Smith, A. J., Dieppe, P., Vernon, K., Porter, M., & Blom, A. W. (2012a). Failure rates of stemmed metal-on-metal hip replacements: Analysis of data from the national joint registry of england and wales. *Lancet (London, England), 379*(9822), 1199-1204. doi:10.1016/S0140-6736(12)60353-5

Smith, A. J., Dieppe, P., Vernon, K., Porter, M., & Blom, A. W. (2012b). Failure rates of stemmed metal-on-metal hip replacements: Analysis of data from the national joint registry of england and wales. *Lancet (London, England), 379*(9822), 1199-1204. doi:10.1016/S0140-6736(12)60353-5

Smith, M., Marcus, P., & Wurtz, L. (2008). Orthopedic issues in pregnancy. *Obstet Cynegol Surv, 63*(2), 103-111.

Soontornpun, A., Choovanichvong, T., & Tongsong, T. (2018). Pregnancy outcomes among women with epilepsy: A retrospective cohort study. *Epilepsy & Behavior: E&B, 82*, 52-56. doi:10.1016/j.yebeh.2018.03.001

Statistics Finland. (2018). History of official statistics of finland - tilastolaitoksen historiaa. Retrieved from http://www.stat.fi/org/tilastokeskus/historia.html

Stea, S., Bordini, B., De Clerico, M., Traina, F., & Toni, A. (2007). Safety of pregnancy and delivery after total hip arthroplasty. *J Womens Health, 16*(9), 1300-1304.

Stern, S. H., Fuchs, M. D., Ganz, S. B., Classi, P., Sculco, T. P., & Salvati, E. A. (1991). Sexual function after total hip arthroplasty. *Clinical Orthopaedics and Related Research,* (269), 228-235.

Stothard, K. J., Tennant, P. W. G., Bell, R., & Rankin, J. (2009). Maternal overweight and obesity and the risk of congenital anomalies: A systematic review and meta-analysis. *Jama, 301*(6), 636-650. doi:10.1001/jama.2009.113

Sugrue, R., & Zera, C. (2018). Pregestational diabetes in pregnancy. *Obstetrics and Gynecology Clinics of North America, 45*(2), 315-331. doi:10.1016/j.ogc.2018.01.002

Swarup, I., Shields, M., Mayer, E. N., Hendow, C. J., Burket, J. C., & Figgie, M. P. (2017). Outcomes after total hip arthroplasty in young patients with osteonecrosis of the hip. *Hip International: The Journal of Clinical and Experimental Research on Hip Pathology and Therapy, 27*(3), 286-292. doi:10.5301/hipint.5000457

Tapnainen, J., Heikinheimo, O., & Mäkikallio, K. (2019). *Naistentaudit ja synnytykset* Duodecim. Retrieved from http://www.oppiportti.fi/op/njs00001

Tata, L. J., Lewis, S. A., McKeever, T. M., Smith, C. J. P., Doyle, P., Smeeth, L., . . . Hubbard, R. B. (2007). A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *American Journal of Respiratory and Critical Care Medicine, 175*(10), 991-997. doi:10.1164/rccm.200611-1641OC

TAYS. (2017). Eettisen toimikunnan toimintaohje. Retrieved from https://www.tays.fi/fi-FI/Tutkimus_ja_kehittaminen/Tutkimus/Eettinen_toimikunta/Toimintaohje/Eettisen_toimikunnan_toimintaohje(50365)

Teerapornpuntakit J, Chanprapaph P, Karoonuthaisiri N, Charoenphandhu N. Site-Specific Onset of Low Bone Density and Correlation of Bone Turnover Markers in Exclusive Breastfeeding Mothers. *Breastfeed Med.* 2017 Jul/Aug;12(6):331-337. doi: 10.1089/bfm.2016.0204.

Teeter, M. G., Yuan, X., Somerville, L. E., MacDonald, S. J., McCalden, R. W., & Naudie, D. D. (2017). Thirteen-year wear rate comparison of highly crosslinked and conventional polyethylene in total hip arthroplasty: Long-term follow-up of a prospective randomized controlled trial. *Canadian Journal of Surgery. Journal Canadien De Chirurgie, 60*(3), 212-216.

Thies-Lagergren, L., Kvist, L. J., Christensson, K., & Hildingsson, I. (2011). No reduction in instrumental vaginal births and no increased risk for adverse perineal outcome in nulliparous women giving birth on a birth seat: Results of a swedish randomized controlled trial. *BMC Pregnancy and Childbirth, 11*, 22. doi:10.1186/1471-2393-11-22

Thies-Lagergren, L., Kvist, L. J., Christensson, K., & Hildingsson, I. (2012). Striving for scientific stringency: A re-analysis of a randomised controlled trial considering first-time mothers' obstetric outcomes in relation to birth position. *BMC Pregnancy and Childbirth, 12*, 135. doi:10.1186/1471-2393-12-135

THL. (2017). Pohjoismaiset raskaudenkeskeytykset - THL. Retrieved from http://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/raskaudenkeskeytykset/pohjoismaiset-raskaudenkeskeytykset

THL. (2018a). Congenital malformations 2014 in finland - THL. Retrieved from http://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/epamuodostumat

THL. (2018b). Epämuodostumat, congenital anomalies in finland. Retrieved from http://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/epamuodostumat

THL. (2018c). Finnish arthroplasty register - statistical report. Retrieved from thl.fi/far

THL. (2018d). Perinataalitilasto – synnyttäjät, synnytykset ja vastasyntyneet - THL. Retrieved from http://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/synnyttajat-synnytykset-ja-vastasyntyneet/perinataalitilasto-synnyttajat-synnytykset-ja-vastasyntyneet

THL. (2018e). Perinatal statistics - parturients, delivers and newborns - THL. Retrieved from http://thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/sexual-and-reproductive-health/parturients-deliveries-and-births/perinatal-statistics-parturients-delivers-and-newborns

THL. (2018f). Pohjoismaiset perinataalitilastot - THL. Retrieved from http://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/synnyttajat-synnytykset-ja-vastasyntyneet/pohjoismaiset-perinataalitilastot

THL. (2018g). Raskaudenkeskeytykset, induced abortions Retrieved from http://thl.fi/fi/tilastot-ja-data/tilastot-aiheittain/seksuaali-ja-lisaantymisterveys/raskaudenkeskeytykset/raskaudenkeskeytykset

Tong, V. T., Kissin, D. M., Bernson, D., Copeland, G., Boulet, S. L., Zhang, Y., . . . England, L. J. (2016). Maternal smoking among women with and without use of assisted reproductive technologies. *Journal of Women's Health (2002), 25*(10), 1066-1072. doi:10.1089/jwh.2015.5662

Torloni, M. R., Betrán, A. P., Daher, S., Widmer, M., Dolan, S. M., Menon, R., . . . Merialdi, M. (2009). Maternal BMI and preterm birth: A systematic review of the literature with meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 22*(11), 957-970. doi:10.3109/14767050903042561

Triclot, P. (2011). Metal-on-metal: History, state of the art (2010). *International Orthopaedics, 35*(2), 201-206. doi:10.1007/s00264-010-1180-8

Tsukanaka, M., Halvorsen, V., Nordsletten, L., EngesæTer, I. Ø, EngesæTer, L. B., Marie Fenstad, A., & Röhrl, S. M. (2016). Implant survival and radiographic outcome of total hip replacement in patients less than 20 years old. *Acta Orthopaedica, 87*(5), 479-484. doi:10.1080/17453674.2016.1212180

Turcksin, R., Bel, S., Galjaard, S., & Devlieger, R. (2014). Maternal obesity and breastfeeding intention, initiation, intensity and duration: A systematic review. *Maternal & Child Nutrition, 10*(2), 166-183. doi:10.1111/j.1740-8709.2012.00439.x

Usadi, R. S., & Merriam, K. S. (2016). Subclinical hypothyroidism: Impact on fertility, obstetric and neonatal outcomes. *Seminars in Reproductive Medicine, 34*(6), 337-342. doi:10.1055/s-0036-1593486

Väisänen, H. (2015). The association between education and induced abortion for three cohorts of adults in finland. *Population Studies, 69*(3), 373-388. doi:10.1080/00324728.2015.1083608

Väisänen, H. (2016). Educational inequalities in repeat abortion: A longitudinal register study in finland 1975-2010. *Journal of Biosocial Science, 48*(6), 820-832. doi:10.1017/S002193201600016X

Väisänen, H., & Murphy, M. (2014). Social inequalities in teenage fertility outcomes: Childbearing and abortion trends of three birth cohorts in finland. *Perspectives on Sexual and Reproductive Health, 46*(2), 109-116. doi:10.1363/46e1314

Varnum, C., Pedersen, A. B., Mäkelä, K., Eskelinen, A., Havelin, L. I., Furnes, O., . . . Overgaard, S. (2015). Increased risk of revision of cementless stemmed total hip arthroplasty with metal-on-metal bearings. *Acta Orthopaedica, 86*(4), 491-497. doi:10.3109/17453674.2015.1023132

Vegel, A. J., Benden, D. M., Borgert, A. J., Kallies, K. J., & Kothari, S. N. (2017). Impact of obesity on cesarean delivery outcomes. *WMJ: Official Publication of the State Medical Society of Wisconsin, 116*(4), 206-209.

Vejen Hansen, A., Ali, Z., Malchau, S. S., Blafoss, J., Pinborg, A., & Ulrik, C. S. (2019). Fertility treatment among women with asthma: A case-control study of 3689 women with live births. *The European Respiratory Journal, 53*(2) doi:10.1183/13993003.00597-2018

Vernini, J. M., Moreli, J. B., Magalhães, C. G., Costa, R. A. A., Rudge, M. V. C., & Calderon, I. M. P. (2016). Maternal and fetal outcomes in pregnancies complicated by overweight and obesity. *Reproductive Health, 13*(1) doi:10.1186/s12978-016-0206-0

Viale, L., Allotey, J., Cheong-See, F., Arroyo-Manzano, D., Mccorry, D., Bagary, M., . . . Thangaratinam, S. (2015). Epilepsy in pregnancy and reproductive outcomes: A systematic review and meta-analysis. *Lancet (London, England), 386*(10006), 1845-1852. doi:10.1016/S0140-6736(15)00045-8

Vikat, B., Kosunen, E., & Rimpela, M. (2002). Risk of postpartum induced abortion in finland: A register-based study. *Perspectives on Sexual & Reproductive Health, 34*(2), 84-90.

Vinet, É, Kuriya, B., Pineau, C. A., Clarke, A. E., & Bernatsky, S. (2013). Induced abortions in women with rheumatoid arthritis receiving methotrexate. *Arthritis Care & Research, 65*(8), 1365-1369. doi:10.1002/acr.22000

Vinet, E., Kuriya, B., Pineau, C. A., Clarke, A. E., & Bernatsky, S. (2013). Induced abortions in women with rheumatoid arthritis receiving methotrexate. *Arthritis Care & Research, 65*(8), 1365-1369.

Vinturache, A., Moledina, N., McDonald, S., Slater, D., & Tough, S. (2014). Pre-pregnancy body mass index (BMI) and delivery outcomes in a canadian population. *BMC Pregnancy and Childbirth, 14* doi:10.1186/s12884-014-0422-y

Visuri, T., & Koskenvuo, M. (1991). Cancer risk after mckee-farrar total hip replacement. *Orthopedics, 14*(2), 137-142.

Visuri, T., Pukkala, E., Paavolainen, P., Pulkkinen, P., & Riska, E. B. (1996). Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clinical Orthopaedics and Related Research,* (329 Suppl), 280.

Vuori, E., & Gissler, M. (2016). Perinatal statistics: Parturients, deliveries and newborns 2015. *National Institute of Health and Welfare,* Retrieved from Thl.fi

Wagner, E. R., Kamath, A. F., Fruth, K. M., Harmsen, W. S., & Berry, D. J. (2016). Effect of body mass index on complications and reoperations after total hip arthroplasty. *The Journal of Bone and Joint Surgery. American Volume, 98*(3), 169-179. doi:10.2106/JBJS.O.00430

Wainwright, C., Theis, J. C., Garneti, N., & Melloh, M. (2011). Age at hip or knee joint replacement surgery predicts likelihood of revision surgery. *The Journal of Bone and Joint Surgery. British Volume, 93*(10), 1411-1415. doi:10.1302/0301-620X.93B10.27100

Wall, P. D. H., Hossain, M., Ganapathi, M., & Andrew, J. G. (2011). Sexual activity and total hip arthroplasty: A survey of patients' and surgeons' perspectives. *Hip International: The Journal of Clinical and Experimental Research on Hip Pathology and Therapy, 21*(2), 199-205. doi:10.5301/HIP.2011.6518

Wallenius, M., Salvesen, K. Å, Daltveit, A. K., & Skomsvoll, J. F. (2014). Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. *Acta Obstetricia Et Gynecologica Scandinavica, 93*(3), 302-307. doi:10.1111/aogs.12324

Wallenius, M., Skomsvoll, J. F., Irgens, L. M., Salvesen, K. Å, Nordvåg, B., Koldingsnes, W., . . . Kvien, T. K. (2011). Fertility in women with chronic inflammatory arthritides. *Rheumatology (Oxford, England), 50*(6), 1162-1167. doi:10.1093/rheumatology/keq458

Wang, B., Yue, D., Liu, B. X., & Guo, W. (2014). Quality of sexual life after total hip arthroplasty in male patients with osteonecrosis of femoral head. *European Journal of Orthopaedic Surgery & Traumatology: Orthopedie Traumatologie, 24*(7), 1217-1221. doi:10.1007/s00590-014-1432-1

Watters, T. S., Eward, W. C., Hallows, R. K., Dodd, L. G., Wellman, S. S., & Bolognesi, M. P. (2010). Pseudotumor with superimposed periprosthetic infection following metal-on-metal total hip arthroplasty: A case report. *The Journal of Bone and Joint Surgery. American Volume, 92*(7), 1666-1669. doi:10.2106/JBJS.I.01208

Weber, B. G. (1992). [Metal-metal total prosthesis of the hip joint: Back to the future]. *Zeitschrift Fur Orthopadie Und Ihre Grenzgebiete, 130*(4), 306-309. doi:10.1055/s-2008-1039623

Weber, B. G. (1996). Experience with the metasul total hip bearing system. *Clinical Orthopaedics and Related Research,* (329 Suppl), 69.

Weiss, B. M., & Hess, O. M. (2000). Pulmonary vascular disease and pregnancy: Current controversies, management strategies, and perspectives. *European Heart Journal, 21*(2), 104-115. doi:10.1053/euhj.1999.1701

Weston, J., Bromley, R., Jackson, C. F., Adab, N., Clayton-Smith, J., Greenhalgh, J., . . . Marson, A. G. (2016). Monotherapy treatment of epilepsy in pregnancy: Congenital malformation outcomes in the child. *The Cochrane Database of Systematic Reviews, 11*, CD010224. doi:10.1002/14651858.CD010224.pub2

WHO. (2018). Abortion worldwide 2017: Uneven progress and unequal access. Retrieved from https://www.guttmacher.org/report/abortion-worldwide-2017

Willert, H., Buchhorn, G. H., Fayyazi, A., Flury, R., Windler, M., Köster, G., & Lohmann, C. H. (2005). Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *The Journal of Bone and Joint Surgery. American Volume, 87*(1), 28-36. doi:10.2106/JBJS.A.02039pp

Williams, M., & Chakravarty, E. F. (2014). Rheumatoid arthritis and pregnancy: Impediments to optimal management of both biologic use before, during and after pregnancy. *Current Opinion in Rheumatology, 26*(3), 341-346. doi:10.1097/BOR.0000000000000046

Wittich, A. C. (1982). Successful pregnancy and delivery following bilateral total hip replacement: Report of case. *The Journal of the American Osteopathic Association, 81*(11), 773-775.

Worldbank. (2018). National fertility rates - open access statistical report. Retrieved from http://www.worldbank.org/

Wu, E. S., Cherian, J. J., Jauregui, J. J., Robinson, K., Harwin, S. F., & Mont, M. A. (2016). Patient-reported outcomes following total hip arthroplasty stratified by body mass index. *Orthopedics, 39*(3), 572. doi:10.3928/01477447-20160404-09

Yazici, Y., Erkan, D., Zuniga, R., Bateman, H., Salvati, E. A., & Magid, S. K. (2003). Pregnancy outcomes following total hip arthroplasty: A preliminary study and review of the literature. *Orthopedics, 26*(1), 75-76.

Yoon, B., Lee, K., Noh, S., Ha, Y., Lee, Y., & Koo, K. (2013). Sexual activity after total hip replacement in korean patients: How they do, what they want, and how to improve. *Clinics in Orthopedic Surgery, 5*(4), 269-277.

Yoon, H. J., Yoo, J. J., Yoon, K. S., Koo, K., & Kim, H. J. (2012). Alumina-on-alumina THA performed in patients younger than 30 years: A 10-year minimum followup study. *Clinical Orthopaedics & Related Research, 470*(12), 3530-3536. doi://dx.doi.org/10.1007/s11999-012-2493-2

Yoshikata H, Tsugawa N, Watanabe Y, Tsuburai T, Chaki O, Hirahara F, Miyagi E, Sakakibara H, Uenishi K, Okano T. 25-Hydroxyvitamin D profiles and maternal bone mass during pregnancy and lactation in Japanese women. *J Bone Miner Metab*. 2019 Aug 20. doi: 10.1007/s00774-019-01032-w.

Zhang, H., Huang, S., Guo, X., Zhao, N., Lu, Y., Chen, M., . . . Cai, W. (2017). A randomised controlled trial in comparing maternal and neonatal outcomes between hands-and-knees delivery position and supine position in china. *Midwifery, 50*, 117-124. doi:10.1016/j.midw.2017.03.022

Zhao, E., Zhang, Y., Zeng, X., & Liu, B. (2015). Association between maternal diabetes mellitus and the risk of congenital malformations: A meta-analysis of cohort studies. *Drug Discoveries & Therapeutics, 9*(4), 274-281. doi:10.5582/ddt.2015.01044

Ziaee, H., Daniel, J., Datta, A. K., Blunt, S., & McMinn, D. J. W. (2007). Transplacental transfer of cobalt and chromium in patients with metal-on-metal hip arthroplasty: A controlled study. *Journal of Bone & Joint Surgery - British Volume, 89*(3), 301-305.

10 ORIGINAL PUBLICATIONS

PUBLICATION
I

Lower birth rate in patients with total hip replacement.

Artama Miia, Skyttä Eerik, Huhtala Heini, Leino Mikko, Kuitunen Ilari, Eskelinen Antti

Acta Orthop. 2016 Oct;87(5):492-6. doi: 10.1080/17453674.2016.1193396. Epub 2016 Jun 1

Acta Orthopaedica

ISSN: 1745-3674 (Print) 1745-3682 (Online) Journal homepage: http://www.tandfonline.com/loi/iort20

Lower birth rate in patients with total hip replacement

Miia Artama, Eerik T Skyttä, Heini Huhtala, Mikko Leino, Ilari Kuitunen & Antti Eskelinen

To cite this article: Miia Artama, Eerik T Skyttä, Heini Huhtala, Mikko Leino, Ilari Kuitunen & Antti Eskelinen (2016) Lower birth rate in patients with total hip replacement, Acta Orthopaedica, 87:5, 492-496, DOI: 10.1080/17453674.2016.1193396

To link to this article: https://doi.org/10.1080/17453674.2016.1193396

Published online: 01 Jun 2016.

OPEN ACCESS

Lower birth rate in patients with total hip replacement

A nationwide population-based study in Finland

Miia ARTAMA [1], Eerik T SKYTTÄ [2], Heini HUHTALA [1], Mikko LEINO [3], Ilari KUITUNEN [3], and Antti ESKELINEN [2]

[1] School of Health Sciences, University of Tampere; [2] Coxa Hospital for Joint Replacement; [3] School of Medicine, University of Tampere, Tampere, Finland.
Correspondence: miia.artama@hotmail.fi
Submitted 2015-08-06. Accepted 2016-04-26.

Background and purpose — There have been few studies on the effect of THR on pregnancy or delivery, and they have mainly been based on small and regional data. We evaluated the birth rate nationwide in patients of fertile age with THR.

Patients and methods — This nationwide population-based cohort study was based on registry data on 5,863 Finnish THR patients who had undergone a THR between 1985 and 2006, and who were aged 15–45 years (females) or 15–50 years (males) at the time of THR. The matched reference cohort consisted of 17,575 sex- and age-matched individuals (3 for each patient) who were alive and resident in Finland at the time of the patient's THR. Birth rate and Cox hazard ratios (HRs) with 95% CI for live births were calculated.

Results — The birth rate after THR was approximately 20–60% lower in the male and female patient groups than in the reference individuals. The probability of having a live birth after THR was lower in female patients than in reference individuals, in all but the oldest age group (40–45 years). The same phenomenon was seen in male patients in all but the youngest age group (15–19 years). Adjustment for potential confounders increased the probability of THR patients having a live birth compared to reference individuals, but the birth rate was still clearly reduced (in men, adjusted HR = 0.80, 95% CI: 0.69–0.92; in women, adjusted HR = 0.56, 95% CI: 0.46–0.68).

Interpretation — THR has a substantial effect on the birth rate of offspring, in both women and men. THR patients had a lower birth rate and probability of having a child after surgery, even after taking possible confounders into account.

Approximately 25% of all total hip replacement (THR) procedures are carried out on younger people, and slightly more than 50% on women (Lucht 2000, Furnes et al. 2001, Puolakka et al. 2001, Malchau et al. 2002).

There have been few studies on the effects of THR on pregnancy or delivery and vice versa. In addition, such studies have been mainly based on small material and regional data (Monaghan et al. 1987, Ostensen 1993, McDowell and Lachiewicz 2001, Boot et al. 2003, Meldrum et al. 2003, Yazici et al. 2003, Ginsel and Pijnenborg 2005, Sierra et al. 2005, Stea et al. 2007). Previous studies have not found any correlation between THR and complications during pregnancy or delivery (McDowell and Lachiewicz 2001, Meldrum et al. 2003, Sierra et al. 2005). Furthermore, neither pregnancy nor delivery has been shown to reduce the survival of the THR (McDowell and Lachiewicz 2001, Meldrum et al. 2003, Sierra et al. 2005, Stea et al. 2007). Previous studies have also suggested that THR is not a contraindication for normal vaginal birth (Monaghan et al. 1987, Ostensen 1993, Meldrum et al. 2003, Yazici et al. 2003, Sierra et al. 2005, Stea et al. 2007). Women of fertile age who have undergone a THR procedure are often concerned about the effect of their hip replacement on pregnancy and delivery (Smith et al. 2008). In addition, sex life can also be limited after THR, at least in patients with rheumatoid arthritis (RA) (Baldursson and Brattström 1979). Previous studies have focused on pregnancy and delivery in women with THR. To the best of our knowledge, there have been no studies that have analyzed birth rate after THR.

We analyzed the effect of THR on birth rate using nationwide population-based registry data. We also assessed whether diabetes mellitus (DM) and RA affect the fertility of patients who have undergone THR. Our hypothesis of a lower birth rate was more sociologically-based than biologically-based. Women with THR may be more concerned about the course of pregnancy, and people with THR may have reduced sexual activity. Furthermore, the effects of the use of bone cement, or metal-on-metal articulation, on semen quality and fertility in men are still unclear.

DOI 10.1080/17453674.2016.1193396

Patients and methods

The study was based on information recorded in 4 national registries in Finland. Information on THRs was obtained from the Finnish Arthroplasty Register, which is part of the mandatory Implant Register maintained by the Finnish National Institute of Health and Welfare. The Arthroplasty Register has information on all primary arthroplasty procedures carried out in Finland (Puolakka et al. 2001) The coverage of the Register is good, and most of the content corresponds well with hospital record data. Currently, over 97% of all implantations are recorded (Finnish Arthroplasty Register 2015).

We included patients who underwent a THR between 1985 and 2006 and who were aged from 15 to 45 years (females) or 15 to 50 years (males) at the time of the THR. Although men are usually fertile long after 50 years of age, we did not include men over 50 years of age at the time of the THR, to avoid having senior THR patients during the follow-up (0–31 years). Information on the reference group without THR was obtained from the mandatory Population Register, which is maintained by the Finnish Population Register Center. For each patient, 3 reference individuals without THRs, who were alive and resident in Finland at the time of the patient's THR, were selected with matching for sex, age, place of residence, and mother tongue. Information on previous live-born children before THR (0 vs. ≥ 1), marital status (never married vs. ever married), emigration, and death for the whole study population was gathered from the Population Register. Information on diabetes mellitus (DM) and rheumatoid arthritis (RA) was obtained from the Social Insurance Institution of Finland, which maintains the register of medical reimbursements due to chronic diseases and includes information on DM and RA. The prerequisite for reimbursement is a medical certificate showing that the diagnosis was based on clinical examination, that it fulfilled international criteria, and that a board-certified medical doctor carried out the examination. If information on the person was not present in the register, he/she was classified as not having these diseases.

We were able to link all the information from these 4 national registers using the unique personal identification number assigned to all residents of Finland.

Statistics

The Cox multiple regression model with hazard ratios (HRs) and 95% confidence intervals was used to evaluate the risk for the first live-born child in patients after THR, in relation to reference individuals without THR. The start of the follow-up was the date of the patient's THR. The date of the THR of the patient was also the start of the follow-up for the corresponding reference individuals. The endpoint of the follow-up was the date of birth of a first live-born child after the start of the follow-up, date of emigration of the patient, date of death of the patient, or the common closing date (January 26, 2011), whichever occurred first.

Stratified analyses were conducted according to age at the start of follow-up (< 20, 20–34, 35–39 and ≥ 40 years), number of live births before THR, marital status, DM, and RA. Separate adjusted multivariable analyses were conducted, which included age at the time of THR, marital status, number of previous live-born children before THR, and DM or RA diagnosis as potential confounding factors. The age at the start of the follow-up was used as a continuous variable in these adjusted analyses. All the analyses were conducted separately for men and women. PASW Statistics for Windows, SPSS version 18.0, and STATA 8.2 were used for the statistical analyses. The subjects registered in the registries were not contacted, so according to Finnish regulations, informed consent was not required.

Results

The THR patient group comprised 3,434 men and 2,429 women, and the reference group comprised 10,299 men and 7,276 women. The mean follow-up time was 11 (0–31) years for male patients and 11 (0–31) years for male reference individuals, and for women the mean follow-up time was 14 (0–31) years for patients and 14 (0–31) years for reference individuals. The mean age at the start of follow-up was 43 (15–50) years in men and 38 (15–46) years in women. During the follow-up, the number of first live-born children after THR was 435 for patients and 2,213 for reference individuals (Table 1).

Birth rate varied according to age at the start of follow-up, according to the number of previous live-born children before THR, and according to marital status (Table 2). However, birth rate was lower in all the patient groups than in reference individuals, in both sexes, and regardless of number of previous children. Male THR patients with DM had a higher birth rate than reference individuals without THR but with DM. The same was seen in male THR patients with RA. In women, the birth rate was lower in THR patients with either DM or RA than in reference individuals. Birth rate was lower in all age groups of the patient population than in reference individuals. These differences were especially obvious in female patients in the 2 youngest age groups and in male patients aged 20–35 years.

The reduced probability of a live-born child when comparing patients with reference individuals could also be seen in Cox regression models (Table 3). Overall, the probability of having a live-born child after THR was lower in male THR patients (HR = 0.69, CI: 0.60–0.79) and female THR patients (HR = 0.47, CI: 0.40–0.55) than in reference individuals, and also in adjusted analyses (for men, adjusted HR (aHR) = 0.80, 95% CI: 0.69–0.92; for women, aHR = 0.56, CI: 0.46–0.68) (Table 3). Female THR patients had a lower probability of having a live-born child than reference individuals, in all but the oldest age group (40–45 years). The same phenomenon was seen in male patients, in all but the youngest age group

Table 1. Numbers of subjects and live births in patients with total hip arthroplasty (THA) and reference individuals without THA according to age at the start of follow-up, number of previous live-born children before THA, marital status, diabetes mellitus diagnosis, and rheumatoid arthritis diagnosis in Finland, 1985–2006

	Men				Women			
	No. of subjects		No. of live births		No. of subjects		No. of live births	
	Patient	Ref.	Patient	Ref.	Patient	Ref.	Patient	Ref.
Age in years at the start of follow-up								
15–19	28	84	6	29	50	150	15	90
20–34	414	1,240	127	571	621	1,847	140	824
35–39	509	1,528	64	257	571	1,722	22	167
40–45	1,151	3,465	36	193	1,187	3,557	4	28
46–50 for men	1,332	3,982	20	54	N/A	N/A	N/A	N/A
No. of previous live-born children before THA								
0	1,101	2,984	95	435	831	1,871	100	552
≥ 1	2,333	7,315	159	669	1,598	5,405	81	557
Marital status								
Never married	887	2,466	32	183	628	1,370	34	190
Ever married	2,547	7,833	222	921	1,801	5,906	147	919
Diabetes mellitus								
Yes	87	174	4	6	35	48	2	4
No	3,347	10,125	250	1,098	2,394	7,228	179	1,105
Rheumatoid arthritis								
Yes	505	86	44	4	811	68	70	6
No	2,929	10,213	210	1,100	1,618	7,208	111	1,103
Total	3,434	10,299	254	1,104	2,429	7,276	181	1,109

N/A: not applicable.

Table 2. Birth rate (per 10,000 person-years) with 95% CI in patients with total hip replacement (THR) and reference individuals without THR according to age at the start of follow-up, number of previous live-born children before THR, marital status, diabetes mellitus diagnosis, and rheumatoid arthritis diagnosis in Finland, 1985–2006

	Men		Women	
	Patient Rate (95% CI)	Reference Rate (95% CI)	Patient Rate (95% CI)	Reference Rate (95% CI)
Age in years at the start of follow-up				
15–19	216 (97–480)	377 (262–542)	216 (130–358)	570 (463–700)
20–34	300 (252–357)	515 (474–559)	165 (140–195)	400 (374–429)
35–39	114 (89–145)	149 (132–169)	25 (16–38)	63 (54–74)
40–45	27 (20–38)	47 (41–54)	2.4 (0.9–6.4)	5.4 (3.7–7.8)
46–50 for men	13 (8.7–21)	12 (8.9–15)	N/A	N/A
Number of previous live-born children				
0	82 (67–100)	145 (132–159)	86 (70–104)	247 (227–268)
≥ 1	60 (51–70)	77 (72–83)	35 (28–44)	71 (65–77)
Marital status				
Never married	36 (25–50)	78 (67–90)	39 (28–55)	116 (101–134)
Ever married	76 (67–87)	99 (93–106)	57 (48–66)	109 (102–116)
Diabetes mellitus				
Yes	52 (19–138)	38 (17–84)	46 (12–185)	70 (26–186)
No	67 (59–76)	95 (90–101)	52 (45–61)	110 (108–117)
Rheumatoid arthritis				
Yes	64 (47–86)	40 (15–108)	53 (42–67.5)	73 (33–163)
No	67 (59–77)	95 (90–101)	52 (43–62)	110 (104–117)
Total	67 (59–75)	95 (89–100)	52 (45–60)	110 (104–116)

(15–19 years). Adjustment for potential confounding factors (age at the start of follow-up, number of live-born children before THR, marital status, DM, and RA) reduced the probability of having a live-born child in THR patients compared to reference individuals. In THR patients with DM or RA, however, HRs were similar.

Discussion

The main result of this population-based study was that THR had a substantial effect on birth rate when comparing THR patients and reference individuals, and in both women and men. THR patients had a lower birth rate and a lower probability of having a child after surgery. Even after taking possible confounding factors into account, THR patients still had a lower probability of having a child, and in women this difference was especially evident (for men, aHR = 0.80; for women, aHR = 0.56). Our study is the first of its kind and gives baseline information about the birth rate of offspring in both women and men who have undergone THR.

The study had some limitations. The identification of patients with DM or RA may have been incomplete. The diagnosis of DM was based on special medication reimbursements due to chronic diseases. Everyone with at least one reimbursement period due to the disease during their lifetime is included in the register. The reimbursement is based on the diagnosis of DM or RA, and therefore DM or RA medications prescribed for other indications are not included in the reimbursements due to these chronic diseases. Furthermore, it is possible that some of the subjects with recently diagnosed DM or RA were not yet included in the register. Also, some DM patients such as diabetes type-II patients are not reimbursed for medication and therefore do not use drugs for their treatment. Such patients were not included in the register. Information on patients who did not want reimbursement for DM or RA medication was not available. In addition, if the diagnosis of DM or RA was made for a permanently institutionalized patient, information on reimbursement would not necessar-

Table 3. Hazard ratio (HR) with 95% CI for a live-born child after total hip replacement (THR) in patients in relation to reference individuals without THR according to various demographic factors, diabetes mellitus diagnosis, and rheumatoid arthritis diagnosis in Finland, 1985–2006

	Men HR (95% CI)	Women HR (95% CI)
Crude	0.69 (0.60–0.79)	0.47 (0.40–0.55)
Adjusted [a]	0.80 (0.69–0.92)	0.56 (0.46–0.68)
Age in years at the start of follow-up		
15–19	0.57 (0.24–1.4)	0.34 (0.20–0.60)
20–34	0.61 (0.50–0.74)	0.43 (0.36–0.51)
35–39	0.74 (0.56–0.97)	0.38 (0.25–0.60)
40–45	0.57 (0.40–0.81)	0.43 (0.15–1.2)
46–50 for men	1.12 (0.67–1.9)	N/A
Number of previous live births before THR		
0	0.58 (0.46–0.72)	0.36 (0.29–0.44)
≥ 1	0.75 (0.63–0.89)	0.48 (0.38–0.61)
Marital status		
Never married	0.48 (0.33–0.70)	0.36 (0.25–0.51)
Ever married	0.74 (0.64–0.86)	0.51 (0.43–0.61)
Diabetes mellitus		
Yes	1.32 (0.37–4.7)	0.64 (0.12–3.5)
No	0.69 (0.60–0.79)	0.47 (0.40–0.55)
Rheumatoid arthritis		
Yes	1.81 (0.65–5.1)	0.84 (0.37–1.9)
No	0.67 (0.58–0.78)	0.44 (0.36–0.54)

HR: hazard ratio. Reference (HR = 1.0) are individuals without THR.
[a] Hazard ratio adjusted for age at the start of follow-up, number of previous live births before THR, marital status, diabetes mellitus, and rheumatoid arthritis.

ily be included in the database. Those patients were probably under-represented in our study. However, the cost of medications for DM and RA is high in Finland, so very few people with DM or RA decline reimbursement for these medications.

Marital status did not confound the effect of THR on birth rate in our study, but it slightly modified the association. As exact information on marital status at the time of THR was not available, information on the first marriage was used. Information on DM and RA diagnosis was obtained at the time of THR. Due to missing information on possible changes in marital status, DM or RA, these factors were not included in the analyses as time-dependent covariates, and residual confounding due to these factors is possible.

We did not have information on possible gynecological or urological procedures, or any other factors that might reduce fertility or cause infertility. Also, no information on spontaneous or induced abortions was available. Exclusion of these factors may have affected residual confounding, so our results should be interpreted with caution.

We restricted age of the study cohort to women aged from 15 to 45 and to men aged from 15 to 50 at the time of THR. Aging affects a woman's reproductive potential through menopause, but the effects of aging on the fertility of a man remain poorly defined (Johnson et al. 2015). However, men over 51 years are still of fertile age. Exclusion of the offspring of men over 50 at the THA may have biased our results, if the birth rate differed substantially between THA patients and reference individuals in this age group.

According to earlier studies, pregnancy and delivery can occur safely after THR (Sierra et al. 2005, Stea et al. 2007). Pregnancy and delivery are not associated with lower function of the prosthesis and the radiographic appearance of the prosthesis is not adversely affected by pregnancy (Ostensen 1993). Pregnancy does not increase the number of early revisions of hip prostheses (Smith et al. 2008), and pregnancy and delivery are not associated with lower survival of hip prostheses. Furthermore, there is no increase in pregnancy-related complications in pregnancy after THR (McDowell and Lachiewicz 2001, Smith et al. 2008). In all these earlier studies, the study groups have been small. In addition, no previous studies have been carried out on the birth rate of offspring of men in partnerships after THR.

One explanation for the lower birth rate in all THR patients might be a lower quality of life in THR patients than in people with no THR (Räsänen et al. 2007). It has been reported that THR patients fared worse in many areas of perceived health (Räsänen et al. 2007). Another study showed that quality of life is similar in THR patients and in people without THR, in most dimensions (Stea et al. 2007). In contrast, it has also been found that people who have a condition that may require THR suffer from a lower quality of life (Sierra et al. 2005, Stea et al. 2007). It has also been reported that THR reduces hip-related problems in the sexual life of RA patients (Baldursson and Brattström 1979). Overall, THR improves quality of life compared to the pre-operational situation in many dimensions, and may therefore increase birth rate as the patient's quality of life improves after surgery.

Having had live-born children before THR affected the birth rate after THR in both men and women. Compared to those who already had children, both patients and reference individuals with no children before surgery had a higher birth rate after surgery. While the birth rate was consistently higher in the reference population, the difference in birth rates between THR patients and their designated references was less pronounced in those who had previously had live-born children. This change in birth rates can also be seen as a change in hazard ratios for a live-born child when comparing THR patients with reference individuals. This could be due to a tendency of the reference group to have reached their planned family size at a younger age because of their higher quality of life.

In summary, patients with THR have a lower birth rate after surgery than people without THR. The most probable reason for this is the underlying hip disease causing a lower quality of life.

MA, ES, HH, ML, and AE had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MA, ES, and AE contributed to the conception and design of the study. ML drafted the manuscript. AE supervised the study. HH was responsible for the statistical analyses. All authors participated in the interpretation of data and in critical revision of the manuscript.

No competing interests declared.

Baldursson H, Brattström H. Sexual difficulties and total hip replacement in rheumatoid arthritis. Scand J Rheumatol 1979; 8 (4): 214-6.

Boot C L, Heyligers I C, Heins K F. Pregnancy and delivery after revised total hip replacement. Orthopedics 2003; 26 (8): 813-4.

Finnish arthroplasty register. Total hip and knee arthroplasty report 2015. National Institute for Health and Welfare, Helsinki 2015. Available at: https://www2.thl.fi/endo/report/#html/welcome. [cited 2015 Dec 18].

Furnes O, Lie S A, Espehaug B, Vollset S E, Engesaeter L B, Havelin L I. Hip disease and the prognosis of total hip replacements. A review of 53,698 primary total hip replacements reported to the Norwegian Arthroplasty Register 1987-99. J Bone Joint Surg (Br) 2001; 83 (4): 579-86.

Ginsel B, Pijnenborg J M. Pregnancy and childbirth after total hip arthroplasty. J Bone Joint Surg (Br) 2005; 87 (12): 1702.

Johnson S L, Dunleavy J, Gemmel N J, Nakagawa S. Consistent age-dependent declines in human semen quality: a systematic review and meta-analysis. Ageing Res Rev 2015;19:23-30.

Lucht U. The Danish Hip Arthroplasty Register. Acta Orthop Scand 2000;71:433-439.

Malchau H, Herberts P, Eisler T, Garellick G, Söderman P. The Swedish Total Hip Replacement Register. J Bone Joint Surg (Am) 2002; 84-A (Suppl 2): 2-20.

McDowell C M, Lachiewicz P F. Pregnancy after total hip arthroplasty. J Bone Joint Surg (Am) 2001; 83-A (10): 1490-4.

Meldrum R, Feinberg J R, Capello W N, Detterline A J. Clinical outcome and incidence of pregnancy after bipolar and total hip arthroplasty in young women. J Arthroplasty 2003; 18 (7): 879-85.

Monaghan J, Lenehan P, Stronge J, Gallagher J. Pregnancy and vaginal delivery following bilateral total hip replacement. Eur J Obstet Gynecol Reprod Biol 1987; 26 (3): 261-4.

Ostensen M. Hip prostheses in women of fertile age. Consequences for sexuality and reproduction. Tidsskr Nor Laegeforen 1993; 113 (12): 1483-5.

Puolakka T J, Pajamäki K J, Halonen P J, Pulkkinen P O, Paavolainen P, Nevalainen J K. The Finnish Arthroplasty Register: report of the hip register. Acta Orthop Scand 2001; 72 (5): 433-41.

Räsänen P, Paavolainen P, Sintonen H, Koivisto AM, Blom M, Ryynänen O P, Roine R P. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. Acta Orthop 2007; 78 (1): 108-15.

Sierra R J, Trousdale R T, Cabanela M E. Pregnancy and childbirth after total hip arthroplasty. J Bone Joint Surg (Br) 2005; 87 (1): 21-4.

Smith M W, Marcus P S, Wurtz L D. Orthopedic issues in pregnancy. Obstet Gynecol Surv 2008; 63 (2): 103-11.

Stea S, Bordini B, De Clerico M, Traina F, Toni A. Safety of pregnancy and delivery after total hip arthroplasty. J Womens Health (Larchmt) 2007; 16 (9): 1300-4.

Yazici Y, Erkan D, Zuniga R, Bateman H, Salvati E A, Magid S K. Pregnancy outcomes following total hip arthroplasty: a preliminary study and review of the literature. Orthopedics 2003 (1); 26: 75-6.

PUBLICATION
II

Induced Abortions Among Women Having Undergone Total Hip Replacement: A Nationwide Register Study in Finland

Kuitunen Ilari, Skyttä Eerik, Eskelinen Antti, Huhtala Heini, Artama Miia.

Scand J Surg. 2019 Sep;108(3):258-264. doi: 10.1177/1457496918812229. Epub 2018 Nov 16.

SJS
SCANDINAVIAN
JOURNAL OF SURGERY

Original Article

INDUCED ABORTIONS AMONG WOMEN HAVING UNDERGONE TOTAL HIP REPLACEMENT: A NATIONWIDE REGISTER STUDY IN FINLAND

I. Kuitunen[1], E. T. Skyttä[2], A. Eskelinen[2], H. Huhtala[3], M. Artama[3,4]

[1] Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland
[2] COXA Hospital for Joint Replacement, Tampere, Finland
[3] Faculty of Social Sciences, University of Tampere, Tampere, Finland
[4] National Institute of Health and Welfare (THL), Tampere, Finland

ABSTRACT

Background and Aims: **No previous studies have analyzed the connection between total hip replacement and induced abortion. We evaluated the nationwide induced abortion rates among women with and without total hip replacement.**

Materials and Methods: **Data for this cohort study were gathered from national registers from 1987 to 2007. All fertile-aged (15–44 years old) females who had undergone primary total hip replacement in Finland were selected. The total hip replacement patient group comprised 1713 women and the reference group 5148 women. Information on all pregnancies for both groups before and after total hip replacement/index date was gathered from the medical birth register and the register of induced abortion. Logistic regression model was used to analyze the adjusted odds ratio for induced abortion. Adjustment was made for age at induced abortion, parity, previous induced abortions, previous deliveries, and marital status.**

Results: **Women had higher induced abortion proportions after total hip replacement (17.9%) compared with women before total hip replacement (14.1%) and the referents (13.9%), but the differences were not statistically significant. Women in the total hip replacement patient group had significantly more induced abortions after total hip replacement due to maternal health issues (14.7%) compared with the referents (2.7%), p = 0.003. Patients in the total hip replacement group were not more likely to have their pregnancy ending in induced abortion than the women in the reference group (odds ratio 1.32, 95% confidence interval 0.89–1.96, p = 0.17). However, in the adjusted analysis, there was a trend for higher risk for pregnancy to end in induced abortion in the total hip**

Correspondence:
Ilari Kuitunen
Faculty of Medicine and Life Sciences
University of Tampere
Ilmarinkatu 31b32
33500 Tampere
Finland
Email: kuitunen.ilari.m@student.uta.fi

Scandinavian Journal of Surgery
1–7

DOI: 10.1177/1457496918812229
journals.sagepub.com/home/sjs
SAGE

replacement group in relation to the reference group (adjusted odds ratio 1.50 (confidence interval 0.99–2.28, p = 0.05).

***Conclusion:* The total hip replacement patient group had higher, but statistically insignificant, induced abortion proportions compared with the reference group before and after the operation. After total hip replacement, the patients were not more likely to have a pregnancy ending in induced abortion. This finding remained statistically insignificant after adjusting with possible confounders.**

Key words: Total hip replacement; orthopedics; joint replacement; induced abortion; reproduction; cohort study; register study; pregnancy; epidemiology

INTRODUCTION

Total hip replacement (THR) is a highly effective surgical procedure (1) that results in major improvements in the patients' quality of life, pain, sleep, physical ability, and sexual function (2–4). The main indications for THR in patients under 30 years of age are rheumatoid arthritis (RA) (36%) and avascular necrosis (23%) (5), whereas indications for overall primary THR for all ages in Finland are primary osteoarthritis (78%) and RA (7%) (6).

In Finland, the total number of primary THR per year has grown from slightly over 5000 in 2000 to over 10,000 in 2017 (7). Of these, almost 60% of patients were female. Every year, almost 500 THRs are carried out on patients under 50. The number of patients in this age group has grown slightly since 2003 (7). In 2007, the incidence of THR for young patients (30–49 years old) was 39 per 100,000 person years and the incidences increased slightly from 1980 to 2007 (8).

A few studies with small sample sizes and regional data have investigated the effects of THR on pregnancies and deliveries and vice versa. According to these previous studies, THR does not seem to be a contraindication for pregnancy or delivery (9, 10). Moreover, neither pregnancy nor delivery decrease implant survival after THR (9–13). Women who have undergone THR seem to have lower fertility rates (14). One reason for the lower fertility rates might be that women have concerns about pregnancy and delivery after THR (9). These findings could therefore implicate reproductive problems or an increased induced abortion (IA) rate.

The rate of IA in Finland was 8.7 per 1000 fertile-aged women (15–49 years old) in 2013 (15), which was the lowest rate in the Nordic countries. In 2013, the IA rate for the Nordic countries was 13.5/1000 fertile-aged women. Although rates of IA have been stable in the Nordic countries for much of the 21st century, a small decline has been seen during the last 2 years (15). Overall, the worldwide rate of IA has been stable (29/1000 fertile-aged women in 2003 versus 28/1000 in 2008) (16). The main indications for IA in Finland are social reasons (91.8%), fetal defects (3.4%), female aged over 40 at the start of the pregnancy (3.1%), and female aged under 17 at the start of the pregnancy (2.7%) (15).

Women with a lower socioeconomic status (SES) have a higher risk for IA compared with those of a higher SES (17). A Brazilian study estimated that women over 40 years of age or unmarried have more IAs than any other group (18). Furthermore, a previous IA may lead to repeat abortion (19, 20). In addition, a short time between delivery and the next pregnancy increases the risk for abortion (21).

To the best of our knowledge, no previous studies have evaluated the relationship between THR and IA. The aim of the present study is therefore to investigate whether women with THR have a higher risk of IA compared with a reference group without THR at the national level.

MATERIALS AND METHODS

In this nationwide register-based retrospective cohort study, data were obtained from five national health registers: the Finnish Arthroplasty Register (FAR), the Register of Induced Abortion (RIA), the Finnish Population Information System, the National Medical Birth Register (MBR), and the register of medical reimbursement (RMR) due to chronic diseases maintained by the Social Insurance Institution of Finland.

The THR patient group consisted of all fertile-aged women (15–44 years old) who had undergone their first primary THR in Finland between 1987 and 2007. The THR patients were identified from the FAR that is maintained by Finnish National Institute for Health and Welfare (THL). The FAR contains information on all hip and knee prostheses carried out in Finland. All the information in the FAR has been collected prospectively. The current (2017) completeness of the register is 95% for primary THR and it matches well with data from the Finnish Hospital Discharge Register (7).

For every THR patient, three reference persons without THR were obtained from the Population Information System maintained by the Finnish Population Register Center. These reference persons were individually matched to THR patients by age, place of residence, and mother tongue. Information on the number of biological children born to the patients and the referents before the end of 2007 was also gathered from the population information system. The index date for the referents was the day their matching patient underwent THR.

Information on IAs from 1987 to 2007 was obtained from the RIA. The RIA contains information on abortion rates and indications, as well as background information on females who have undergone IA. The overall coverage of the RIA is high, as is the validity of most of the variables. However, some problems have been reported with the coverage of SES and gestational age (22).

Information on pregnancies from 1987 to 2007 was obtained from the MBR. The register contains information on all births after gestational week 22 + 0 or birth weight over 500 g. The MBR also contains information on maternal background characteristics, pregnancy history, pregnancy and delivery diagnoses, and neonatal data up to 7 days after birth. The MBR has high coverage and good quality of data, which has improved over time (23).

The RMR contains information on reimbursable costs due to chronic diseases. For reimbursement, a medical certificate issued by a certified doctor is required. Information on RA was gathered for study population and participants with no record of RA reimbursement in the RMR were classified as not having the disease.

The start of the abortion follow-up was the 1st of January 1987 or the day the patient turned 15 years old, whichever occurred last. The endpoints for the abortion follow-up were the 31st of December 2007, or the date of the patients' 45th birthday, emigration, or death, whichever occurred first.

ETHICS

All the data were linked with the unique identification number assigned to all residents of Finland. In accordance with Finnish regulations, no informed written consent was required because participants in the study were not contacted individually. Permission for the data use was granted by the register holders. Permission number: THL/599/5.05.00/2010.

STATISTICS

The logistic regression model was used to evaluate whether THR increased the risk of IA. Both unadjusted and adjusted odds ratios (ORs) with 95% confidence interval (CI) were calculated. In the adjusted model, the following potential confounders or modifiers were adjusted for age at time of abortion, parity, previous IAs, previous deliveries, and marital status.

Comparisons between the groups both before and after the THR/index date on abortion rates as well as on indications for abortions were carried out. Chi-square test or Fischer's exact test was used to analyze categorized variables between the THR patient group and the reference group. The CI for the difference between two proportions (later as proportion difference = PD) was used to evaluate the intergroup differences before THR and after THR in the THR patient group and before and after index date in the reference group. Statistical analyses were conducted with IBM SPSS for windows version 22 software. P-values under 0.05 were considered statistically significant.

TABLE 1

Background characteristics of study population.

	Women with THR		Women without THR	
Age at the start* of the abortion follow-up				
15–19	340	19.8	1017	19.8
20–24	353	20.6	1062	20.6
25–29	335	19.6	1009	19.5
30–34	361	21.1	1072	20.8
35–39	230	13.4	703	13.7
40–44	94	5.5	285	5.5
Age at THR/index date				
15–19	39	2.3	117	2.3
20–24	80	4.7	236	4.6
25–29	155	9.0	465	9.0
30–34	230	13.4	684	13.3
35–39	435	25.4	1310	25.4
40–44	774	45.2	2336	45.4
Marital status				
Ever married	1238	72.3	4059	21.2
Never married	475	27.7	1089	78.8
Nulliparous at the start of the abortion follow-up	979	57.2	2706	52.6
Follow-up time (years + SD)				
Before THR/index date	9.8	5.9	9.8	5.9
After THR/index date	5.2	4.5	5.3	4.6
Chronic diseases				
Rheumatoid arthritis	521	30.4	42	0.8
Diabetes mellitus	28	1.6	33	0.6
Epilepsy	6	0.4	12	0.2
Major mental disease	3	0.2	8	0.2

THR: total hip replacement; index date: date of the operation in the THR patient group and the same date for matching referents; start of the abortion follow-up: day of the 15th birthday or 1st of January 1987, whichever came first.

RESULTS

The total number of female participants in this study was 6861. Among these, a total of 6608 pregnancies and 885 (13.4%) IAs occurred. The THR patient group comprised 1713 women, with 1274 pregnancies and 187 (14.7%) IAs. Of these, 199 pregnancies and 35 (17.9%) IAs occurred after the THR. The reference group comprised 5148 women with 5334 pregnancies and 698 (13.1%) IAs. Of these, 1308 pregnancies and 182 (13.9%) IAs occurred after the index date. Mean age at the beginning of the abortion follow-up was 27.4 years and mean age at the THR/index date was 37.3 years in both groups. The basic demographics of the patients and the referents are presented in Table 1.

In the patient group, the abortion rate was 9.0/1000 person years (pyrs) before the THR and 3.9/1000 pyrs after the THR. In the reference group, the rates were 10.2/1000 pyrs before the index date and 6.6/1000 pyrs after the index date. In the patient group, abortion rates were 17/100 births before the index date and 21/100 births after the index date. In the reference group, the abortion rate was 15/100 births before the index date and 16/100 births after the index date.

TABLE 2

Total number of abortions for women with and without total hip replacement (THR) before and after THR/index date in Finland between 1987 and 2007.

	Women with THR				Women without THR			
	Before THR		After THR		Before the index date		After the index date	
	n = 152	%	n = 35	%	n = 516	%	n = 182	%
Previous pregnancies								
0	46	31.1	9	25.7	176	34.3	37	20.4
1+	102	68.9	26	74.3	337	65.7	144	79.6
Previous abortions								
0	95	63.8	28	80.0	340	66.3	115	63.5
1+	54	36.2	7	20.0	173	33.7	66	36.5
Previous births								
0	57	38.0	12	34.3	229	44.4	49	26.9
1+	93	62.0	23	65.7	287	55.6	133	73.1
Induced abortion indications								
Social reasons	118	77.6	24	68.6	447	86.6	126	69.2
Age[a]	5	3.3	4	11.4	31	6.0	23	12.6
Maternal health	17	11.2	5	14.3	14	2.7	5	2.7
Fetal health	6	3.9	1	2.9	13	2.5	12	6.6
Over 4 previous births	6	3.9	1	2.9	11	2.1	16	8.8
Socioeconomic status	37	24.3	18	51.4	141	31.2	95	52.2
Upper white-collar	1	2.7	3	16.7	14	8.7	20	21.1
Lower white-collar	19	51.4	6	33.3	57	35.4	38	40.0
Blue-collar	6	16.2	5	27.8	34	21.1	16	16.8
Other[b]	11	29.7	4	22.2	36	22.4	21	22.1
Age at THR/index date								
Under 20	0	0.0	4	11.4	3	0.6	15	8.2
20–24	4	2.6	4	11.4	35	6.8	27	14.8
25–29	16	10.5	3	8.6	58	11.2	45	24.7
30–34	30	19.7	12	34.3	100	19.4	37	20.3
35–39	35	23.0	9	25.7	117	22.7	43	23.6
40 or more	67	44.1	3	8.6	203	39.3	15	8.2
Age at the time of abortion								
Under 20	12	7.9	1	2.9	49	9.5	5	2.7
20–24	29	19.1	4	11.4	105	20.3	13	7.1
25–29	40	26.3	4	11.4	119	23.1	30	16.5
30–34	37	24.3	5	14.3	136	26.4	40	22.0
35–39	29	19.1	13	37.1	79	15.3	58	31.9
40 or more	5	3.3	8	22.9	28	5.4	36	19.8
Marital status								
Never married	51	33.6	12	34.3	159	30.8	46	25.3
Ever married[c]	101	66.4	23	65.7	357	69.2	136	74.7
Rheumatoid arthritis								
No	131	86.2	24	68.6	509	98.6	182	100.0
Yes	21	13.8	11	31.4	7	1.4	0	0.0

Index date: date of the operation in the THR patient group and the same date for matching referents.
[a]Age under 18 or over 40.
[b]Includes students and non-workers.
[c]Only the date of the first marriage is known. No information about divorces or new marriages.

IA indications varied slightly between the women with and without THR (Table 2). More abortions were carried out due to maternal health reasons in the THR patient group. The rate of the first abortion was higher after THR compared with rates before the THR and the reference group. Interestingly, married women seemed to have fewer abortions after THR than unmarried women.

Before the THR/index date, there were 152 (14.1%) IAs among the THR patient group and 516 (12.8%) in the reference group, p = 0.25. After the THR/index date, the THR patient group had 35 (17.9%) IAs and the reference group 182 (13.9%), p = 0.17. In the THR patient group, number of IAs varied from 152 (14.1%) before the THR to 35 (17.9%) after THR (PD = 3.5, CI −1.7 to 9.7). In the reference group, number of IAs before the index date were 516 (12.8%) and 182 after the index date (13.9%), PD = 1.1, CI −1.0 to 3.3. Median time after the THR to IA was 4.0 (range 0.1–20.4) years in the THR patient group and before the THR, the

TABLE 3

Proportions of pregnancies ending in induced abortion with 95% confidence interval (CI) among women with and without total hip replacement (THR) before and after THR/index date in Finland between 1987 and 2007.

	Women with THR				Women without THR			
	Before THR pregnancies		After THR pregnancies		Before the index date pregnancies		After the index date pregnancies	
	%	CI	%	CI	%	CI	%	CI
Previous pregnancies								
0	14.7	10.8–18.6	17.0	8.7–25.3	15.3	13.2–17.3	12.3	8.3–16.2
1+	13.5	11.1–15.9	17.8	11.8–23.8	11.8	10.7–13.0	14.4	12.0–16.7
Previous abortions								
0	11.0	8.9–13.1	16.2	10.8–21.6	10.2	9.1–11.2	10.7	8.7–12.6
1+	41.5	33.1–50.0	36.8	23.1–50.6	39.6	35.0–44.2	36.7	27.8–45.5
Previous births								
0	13.5	10.2–16.8	16.2	8.9–23.6	15.1	13.3–16.9	11.9	8.6–15.2
1+	14.4	11.7–17.1	18.4	11.9–24.9	11.6	10.3–12.8	14.9	12.4–17.4
Age at the time of abortion								
15–29	46.2	27.0–65.3	100.0	0.0–100.0	55.1	44.7–65.4	50.0	6.2–93.8
20–24	20.1	13.6–26.7	28.6	15.4–41.8	19.8	16.4–23.2	18.1	8.2–27.9
25–29	10.6	7.5–13.8	11.4	3.8–19.1	8.5	7.0–10.0	11.0	7.1–27.9
30–34	10.1	7.0–13.2	8.1	2.5–13.6	10.0	8.4–11.6	9.2	6.3–12.0
35–39	19.9	13.4–26.3	22.4	13.3–31.6	14.2	11.3–17.1	15.9	11.8–20.0
40–44	31.3	8.5–54.0	27.6	15.9–39.3	30.8	21.3–40.3	23.7	15.9–31.4
Marital status								
Never married	31.5	24.5–38.9	38.7	25.7–51.7	28.3	24.6–32.0	19.5	13.9–25.1
Ever married	11.1	9.0–13.1	13.7	8.7–18.7	10.3	9.3–11.3	12.7	10.6–14.8
Rheumatoid arthritis								
No	15.0	12.6–17.4	20.3	13.4–27.3	12.8	11.7–13.8	14.0	12.0–16.0
Yes	10.4	6.2–14.7	13.6	7.0–20.1	17.1	5.6–28.6	0.0	0.0–0.0

Index date: date of the operation in the THR patient group and the same date for matching referents.

median time from IA to THR was 8.4 years (0.2–20.5). Median times in the reference group were 3.9 years (0.0–19.7) after the index date and 7.1 years (0.0–20.7) before the index date.

Women in the THR patient group were more likely to undergo their first IA after THR rather than before THR, or women in the reference group. Women in the youngest and the oldest age group had higher IA proportions than those in the moderate age groups (Table 3).

Unadjusted OR for pregnancy ending in IA in the THR patient group after index date was 1.32 (CI 0.89–1.96), $p = 0.17$, in relation to the reference group (Table 4). When adjusted with the variables of marital status, age (<20 or >39), previous IAs, and previous deliveries, there was a trend for higher risk for pregnancy to end in IA in the THR group in relation to the reference group (OR 1.50, CI 0.99–2.28; $p = 0.05$).

DISCUSSION

Our study showed no increase in the risk of pregnancy ending in IA in women with THR compared with women in the reference group. When adjusting for available confounders, such as age, marital status, previous deliveries, and abortions, the risk for abortion was increased in relation to the reference group but remained non-significant. More abortions were carried out due to maternal health reasons in the THR patient group than in the reference group.

No differences in IA proportions between the groups were observed when the THR patients were compared with the referents. The IA proportions in all groups were similar to the overall national abortion proportion in 2015 (14.5%). IA rates in the THR patient group were lower compared with the reference group and national rates. This finding was due to the lower number of pregnancies per woman in the THR patient group. Our previous study showed that women have lower birth rates after THR (14).

Since no previous studies have analyzed the connection between THR and IA, we must evaluate the effect of other possible factors. Women with THR had lower SES than the referents. Low SES is a risk factor for IA. Women with a lower educational level or income have a higher rate of IA when compared with women with a higher educational level and income (24, 25). The same effect was seen in our study population where blue-collar workers had higher IA numbers than persons with a higher SES. Although THR patients had lower SES, our study showed no increase in risk for IA in the THR group. However, the number of persons with missing information on SES was high in our study.

Previous IA was a high risk factor for IA in this study. Previous studies verify evidence on repeat IA, where the decision to have a second IA is easier after a previous IA (26). The incidence of repeated IAs is decreasing, however (27). After THR, women were

TABLE 4

Odds ratios (ORs) with 95% confidence interval (CI) for pregnancy ending in induced abortion of women with total hip replacement (THR) in relation to the reference cohort of women without THR before and after THR/index date, Finland 1987–2007.

	Before the index date			After the index date		
	Univariate OR	95% CI	p-value	Univariate OR	95% CI	p-value
THR patient group	1.12	0.92–1.36	0.25	1.32	0.89–1.96	0.17
Age[a]	5.51	4.16–7.29	<0.001	2.42	1.69–3.47	<0.001
Never married	3.50	2.91–4.23	<0.001	1.89	1.35–2.64	<0.001
Previous delivery	0.80	0.68–0.95	0.008	1.26	0.92–1.73	0.15
Previous abortion	5.79	4.76–7.04	<0.001	4.49	3.20–6.28	<0.001
Adjusted[b] OR for patient group	1.09	0.88–1.34	0.46	1.50	0.99–2.28	0.06

Index date: date of the operation in THR patient group and the same date for matching referents.
[a]Age less than 20 or 40 or more.
[b]Adjusted by all variables above.

more likely to have their first IA, which may indicate that THR might increase the IA risk.

In the THR patient group, there were more abortions both before and after THR due to maternal health indications than in the referents. Women with THR might have concerns about pregnancy, but the risk of IA was not increased (9). There is no evidence of THR complicating pregnancy or affecting pregnancy outcome (9, 10, 13). The THR patients might have had more baseline diseases compared with the referents. Some diseases are known to increase IA rates. For example, women using psychotropic medication or biological RA medication have increased abortion rates (28, 29). This finding could not, however, be identified in our present study due to the small incidences of chronic diseases (except RA) and the information on exact medications was not available.

This is the first study that has evaluated the relationship between THR and IA. One of the strengths of the study is the large, nationwide study population with long follow-up. Our study also compares the IA rates before and after THR. Another strength of the study is the high quality of the register data (6, 23). Our study provides nationwide population-based findings that include a large and comprehensive study population of THR patients and the reference cohorts. Furthermore, the register-based approach eliminates possible recall-bias, that is, possible previous IAs were identified from reliable registers, not with questionnaires.

Although the register data had high coverage and validity in most variables, information on SES was not fully available for this study. For example, data on the SES of only 34.1% of the participants were available. Moreover, even though the coverage was better in the MBR than in the RIA, it was still not possible to calculate reliable abortion ratios for each SES group or use them as a part of the logistic model. In addition, information on the marital status of the women at the exact time of the abortion was not available. Instead, we only had information on whether the women had ever been married.

CONCLUSION

Further studies are needed to confirm the clinical significance of these novel findings. This study shows that THR does not seem to be an independent risk factor for pregnancy ending in IA, although maternal health issues were a more common IA indication in the THR patient group. Further studies are needed to provide information on pregnancies and deliveries after THR.

ACKNOWLEDGEMENT

The authors would like to thank Mr Peter Heath MA for the language editing of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Competitive Research Funding of Pirkanmaa Hospital District, Tampere, Finland, representing governmental funding.

ORCID ID

Ilari Kuitunen https://orcid.org/0000-0001-8178-9610

REFERENCES

1. Harris WH, Sledge CB: Total hip and total knee replacement. N Engl J Med 1990;323:725–731.
2. Rissanen P, Aro S, Slatis P et al: Health and quality of life before and after hip or knee arthroplasty. J Arthroplasty 1995;10:169–175.
3. Klit J: Results of total joint arthroplasty and joint preserving surgery in younger patients evaluated by alternative outcome measures. Dan Med J 2014;6:B4836.
4. Montin L, Leino-Kilpi H, Suominen T et al: A systematic review of empirical studies between 1966 and 2005 of patient outcomes of total hip arthroplasty and related factors. J Clin Nurs 2008;17:40–45.
5. Adelani MA, Keeney JA, Palisch A et al: Has total hip arthroplasty in patients 30 years or younger improved? A systematic review. Clin Orthop Relat Res 2013;471:2595–2601.
6. Puolakka T, Pajamaki K, Halonen P et al: The Finnish Arthroplasty Register: Report of the hip register. Acta Orthop Scandinavia 2001;72:433–441.

7. Open access statistical report of the Finnish Arthroplasty Register. National Institute for Health and Welfare (THL), www.thl.fi/far (accessed 10 August 2018).
8. Skytta ET, Jarkko L, Eskelinen A et al: Increasing incidence of hip arthroplasty for primary osteoarthritis in 30- to 59-year-old patients. Acta Orthop 2011;82:1–5.
9. Sierra R, Trousdale R, Cabanela M: Pregnancy and childbirth after total hip arthroplasty. J Bone Joint Surg Br 2005;87:21–24.
10. Stea S, Bordini B, De Clerico M et al: Safety of pregnancy and delivery after total hip arthroplasty. J Womens Health 2007;16:1300–1304.
11. Meldrum R, Feinberg J, Capello W et al: Clinical outcome and incidence of pregnancy after bipolar and total hip arthroplasty in young women. J Arthroplasty 2003;18:879–885.
12. McDowell C, Lachiewicz P: Pregnancy after total hip arthroplasty. J Bone Joint Surg Am 2001;83:1490–1494.
13. Maffulli N, Del Buono A, Denaro V: Hip artroplasty: A transient reason not to be pregnant. Surg 2012;10:347–349.
14. Artama M, Skytta ET, Huhtala H et al: Lower birth rate in patients with total hip replacement. Acta Orthop 2016;87:492–496.
15. Heino A, Gissler M: Induced abortions in the Nordic countries 2013. Statistical Report, THL 2015, http://urn.fi/URN:NBN:fi-fe201503262027 (accessed 8 March 2018).
16. Guttmacher Institute. Facts on induced abortion worldwide. World Health Organisation, 2012, https://www.guttmacher.org/sites/default/files/pdfs/pubs/fb_IAW.pdf (2012, accessed 8 March 2018).
17. Jones RK, Kavanaugh ML. Changes in abortion rates between 2000 and 2008 and lifetime incidence of abortion. Obstet Gynecol 2011;117:1358–1366.
18. Souza MG, Fusco CLB, Andreoni SA et al: Prevalence and sociodemographic characteristics of women with induced abortion in a population sample of Sao Paulo, Brazil. Rev Bras Epidemiol 2014;17:297–312.
19. Heikinheimo O, Gissler M, Suhonen S: Age, parity, history of abortion and contraceptive choices affect the risk of repeat abortion. Contraception 2008;78:149–154.
20. Heikinheimo O, Gissler M, Suhonen S: Can the outcome of the next pregnancy be predicted at the time of induced abortion? Hum Reprod 2009;24:820–826.
21. Vikat B, Kosunen E, Rimpela M: Risk of postpartum induced abortion in Finland: A register-based study. Perspect Sex Reprod Health 2002;34:84–90.
22. Gissler M, Ulander VM, Hemminki E et al: Declining induced abortion rate in Finland: Data quality of the Finnish abortion register. Int J Epidemiol 1996;25:376–380.
23. Gissler M, Shelley J: Quality of data on subsequent events in a routine Medical Birth Register. Med Inform Internet Med 2002;23:33–38.
24. Perez G, Ruiz-Munoz D, Gotsens M et al: Social and economic inequalities in induced abortion in Spain as a function of individual and contextual factors. Eur J Public Health 2014;24:162–169.
25. Perez G, Garcia-Subirats I, Rodriguez-Sanz M et al: Trends in inequalities in induced abortion according to educational level among urban women. J Urban Health 2010;87:524–530.
26. Skjeldestad FE: The incidence of repeat induced abortion—A prospective cohort study. Acta Obstet Gynecol Scand 1994;73:706–710.
27. Laanpere M, Ringmets I, Part K et al: Abortion trends from 1996 to 2011 in Estonia: Special emphasis on repeat abortion. BMC Womens Health 2014;14:81.
28. Vinet E, Kuriya B, Pineau CA et al: Induced abortions in women with rheumatoid arthritis receiving methotrexate. Arthritis Care Res 2013;65:1365–1369.
29. Gissler M, Artama M, Ritvanen A et al: Use of psychotropic drugs before pregnancy and the risk for induced abortion: Population-based register-data from Finland 1996–2006. BMC Public Health 2010;10:383.

Received: March 21, 2018
Accepted: October 3, 2018

PUBLICATION
III

Pregnancy outcome in women after total hip replacement: a population-based study.

Kuitunen Ilari, Artama Miia, Eskelinen Antti, Skyttä Eerik, Huhtala Heini, Uotila Jukka.

Eur J Obstet Gynecol Reprod Biol. 2019 Jul;238:143-147. doi: 10.1016/j.ejogrb.2019.05.020.
Epub 2019 May 20.

European Journal of Obstetrics & Gynecology and Reproductive Biology 238 (2019) 143–147

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Pregnancy outcome in women after total hip replacement: A population-based study

Ilari Kuitunen[a,*], Miia Artama[b,c], Antti Eskelinen[d], Eerik T. Skyttä[d], Heini Huhtala[b], Jukka Uotila[a,e]

[a] *Faculty of Medicine and Health Technologies, Tampere University, Tampere, Finland*
[b] *Faculty of Social Sciences, Tampere University, Tampere, Finland*
[c] *National Institute of Health and Welfare, Tampere, Finland*
[d] *COXA Hospital for Joint Replacement and Faculty of Medicine and Health Technologies, Tampere University, Tampere, Finland*
[e] *Tampere University Hospital, Department of Gynecology and Obstetrics, Tampere, Finland*

A R T I C L E I N F O

Article history:
Received 14 May 2019
Accepted 17 May 2019
Available online xxx

Keywords:
Total hip replacement
Pregnancy
Birth outcome
Delivery method
Register study

A B S T R A C T

Objective: Only a few small studies have been published on pregnancies after total hip replacement (THR), and they have reported no adverse pregnancy outcomes after THR. The aim of our study was to evaluate whether maternal THR affects pregnancy outcomes on a population-based level.
Study Design: Data for this nationwide register-based cohort study have been collected from four national registries in Finland from 1980 to 2007. All females who had undergone THR during that period formed the patient group, and three controls for each patient without THR were selected. Patient group comprised 2429 women, 719 (29.6%) of whom had 1190 pregnancies ending in singleton deliveries. Of those births, 986 were before THR and 204 after THR. The control group comprised 7276 women, 2805 (38.6%) of whom had 5112 pregnancies ending in singleton deliveries, 3695 occurred before the index date (time point when THR took place within the patient group) and 1417 after. Logistic regression model was used to analyze univariable and adjusted odds ratios (aOR) for adverse neonatal outcomes after maternal THR compared with controls. Data were adjusted using the following variables: maternal age, smoking, rheumatoid arthritis.
Results: Stillbirth was more common in the patient group compared with control group 4 (2.0%) vs 8 (0.6%) p = 0.02. Moreover, neonates in the patient group were more likely to be born preterm (aOR 3.58, p=<0.001), small for gestational age (aOR 2.83, p = 0.006) and low birthweight (aOR 4.79, p=<0.001), compared to control group. Trial of labor more likely ended in emergency cesarean section in the patient group than in the control group 39 (28.9%) vs 150 (11.6%), p=<0.001. Adverse pregnancy outcome was more common after THR also when compared to pregnancies before THR.
Conclusions: Neonates born after maternal total hip replacement have an increased risk of stillbirth, small for gestational age, low birthweight and preterm birth. Trial of labor is more likely to end in emergency cesarean section.

Introduction

Total hip replacement (THR) is a highly effective operation for decreasing pain and improving quality of life in affected individuals [1]. The most common indications for THR in fertile-aged patients are rheumatoid arthritis (RA), avascular necrosis of the femoral head and developmental dysplasia of the hip [2,3]. In Finland, the annual incidence of primary THR among 30–39 year olds was 59.5 per 100 000 person years in 2007 [4]. The prevalence of THR in Sweden in 1999 was 12 per 100 000 women aged under 40 years and 19 per 100 000 in 2012 [5]. In the United States, it has been estimated that the annual primary THR rate in the less than 45 years old group could possibly increase 3-fold by 2030 compared with 2006 rates [6].

There have only been a few studies that have evaluated the effect of previous THR on later pregnancy and delivery or vice versa. The results of these previous studies have not shown an increased risk for complications in delivery after THR, although the numbers of included patients in these studies have been small (n = 10–50) [7–14]. Interestingly, some of these studies have

* Corresponding author at: Arvo Ylpön katu 34, 33104, Tampere, Finland.
E-mail address: ilari.kuitunen@tuni.fi (I. Kuitunen).

https://doi.org/10.1016/j.ejogrb.2019.05.020

reported an increased rate of cesarean sections (CS) after THR [10,13,15].

Some studies have raised concerns regarding elevated fetal blood metal ion (chromium and cobalt) levels in women with metal-on-metal hip replacements and the possible passage of the metal ions to the fetus via the placenta [16–18]. Most of the case reports, however, have not shown any teratogenic impact, despite elevated placental blood metal ion levels [18–20]. Two case reports have described a neonate with high metal ion levels combined with congenital anomalies [21]. Considering the previous literature, women may still have concerns regarding pregnancy and vaginal delivery after THR operation [11].

The aim of this present study was to evaluate the effect of THR on the delivery and health of neonates on a population-based level using data routinely recorded into national health registers in Finland.

Materials and methods

The study population in this register-based nationwide cohort study was gathered from four different national registers in Finland. Information on all women aged 15 to 45 years who had undergone primary THR between 1980 and 2007 was retrieved from the Finnish Arthroplasty Register and included in this study (n = 2429 women with primary THRs). The register was established in 1980 and is maintained by the National Institute for Health and Welfare. The coverage of the register has been high over the years, especially with regard to primary THR (approximately 95%), and it matches well with the hospital discharge register data [22]. Based on the bearing material, the type of implant was categorized as either metal-on-metal or not metal-on-metal.

For each patient included in the patient group, three control women without THR matched by age at the time of THR and place of residence were obtained from the Finnish Population Information System maintained by the Population Register Centre and formed the control group (n = 7276 control women without THR). The start of the follow-up was the date of THR operation in the THR group and the operation date was the index date for the matching controls. The common closing date for this study was 31st December 2007.

In this study, information on singleton pregnancies and deliveries for both groups was gathered from the national Medical Birth Register, which was established in 1987. The register is maintained by the National Institute for Health and Welfare and contains information on all pregnancies ending in birth or stillbirth after gestational week 22 and neonates weighing over 500 g. The Medical Birth Register also contains the background characteristics of the pregnancies and basic information on deliveries and neonate outcome up to hospital discharge or seven days postpartum [23].

Of the 2429 women in the patient group, 719 (29.6%) had 1190 pregnancies ending in singleton deliveries. Of these, 575 women had 986 singleton deliveries prior to THR, and 144 women had 204 singleton deliveries after THR. The control group comprised 7276 women, 2805 (38.6%) of whom had 5112 pregnancies ending in singleton deliveries. Of these, a total of 1893 women had 3695 singleton deliveries before the index date, and 912 women had 1417 singleton deliveries after the index date. The deliveries after THR/index date were included in the analysis. In addition, a subgroup comparison in the patient group was performed for before and after THR deliveries (Fig. 1).

Information on long-term chronic diseases was obtained from the Register of Medical Reimbursements that is maintained by the Social Insurance Institution of Finland and contains information on reimbursable medical costs for chronic diseases. Reimbursements for medical costs are granted with a medical certificate issued by a licensed doctor. Information on the most common long-term disease, RA, among the study population was obtained, and those persons who did not have a reimbursement for RA medication in the register were classified as not having RA.

Standard deviations (SD) for birth weight and birth length were calculated by using the new Finnish growth references for male and female children and adolescents [24]. A SD of less than −2.0 from mean was considered as small for gestational age (SGA), and a SD greater than +2.0 from mean was considered as large for gestational age (LGA). Standard deviations were calculated for all neonates. Neonates born before gestational week 37 + 0 were defined as preterm. Neonates weighing less than 2 500 g were defined as low birthweight (LBW).

All the singleton pregnancies were observed and compared between the groups. Chi-squared test was used to analyze intergroup differences in the categorical variables between the patient group and the control group. A p-value under 0.05 was considered statistically significant. Confidence intervals (95% CI) for the difference of the two proportions were used when

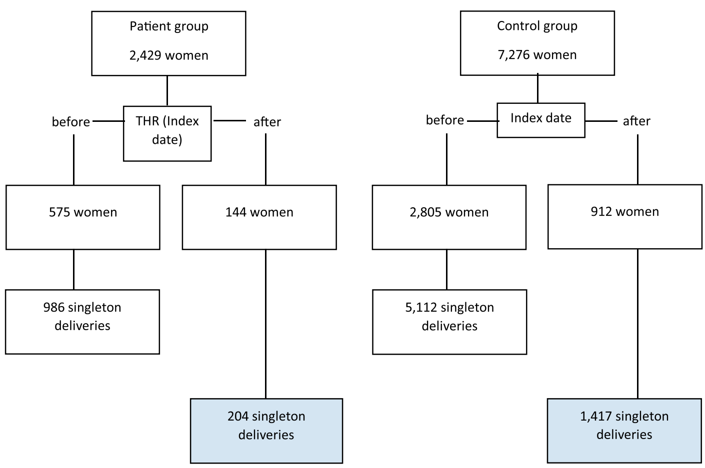


Fig. 1. Flow chart of study population. Index date is the date of THR. Deliveries of the patient group were classified as taking place before or after THR, and likewise the deliveries of the control group were matched according to the index date.

comparing before and after THR proportions in the patient group. Means with SD's were calculated for normally distributed variables and medians with interquartile ranges for non-normally distributed variables. Logistic regression model was used to calculate odds ratios (OR) with 95% CI to compare adverse pregnancy outcomes between the patient and control groups. The following covariates from the available variates in the registers were included and selected based on the previous literature in the adjusted model: maternal age, smoking during pregnancy and maternal RA. Statistical analyses were performed using IBM SPSS for Windows, version 24.0 software.

All the data were linked by using the individual personal identification code that is issued to all permanent residents of Finland. No written consent was required since none of the participants were contacted, and hence no approval from the local ethical committee was required. However, our study protocol did undergo ethical evaluation by the National Institute for Health and Welfare in order to gain access to register data, permission number: THL/599/5.05.00/2010.

Results

Women in the patient group were older at the time of delivery compared with the control group. A higher proportion of women had their first pregnancy after THR in the patient group. In 42% of the deliveries in the patient group, the mother had RA. Baseline information and background characteristics of the pregnant women are presented in Table 1.

Stillbirth was more common in the patient group compared with the control group (Table 2). In the patient group, neonates had a lower birthweight and birth length. The neonates born in this group were also more likely to be born preterm compared with the control group. In addition, neonates born after THR also had higher LBW and SGA proportions and needed more neonatal intensive care treatment and phototherapy compared with the control group (Table 2). When these findings were adjusted with potential confounders, THR remained an independent risk factor in the patient group for preterm birth, LBW and SGA, but not for stillbirth (Table 3).

The pregnancies in the patient group were also compared to pregnancies before THR. Our findings showed adverse pregnancy outcomes were more common after THR than before THR. Moreover, the rates of stillbirth (2.0% vs 0.3%, p = 0.004), SGA neonates (8.3% vs 3.3%, p = 0.001) and preterm births (13.7% vs 7.1%, p = 0.001) were all found to be higher after THR.

In subgroup analysis, deliveries with maternal metal-on-metal THRs (n = 16) were compared with deliveries with non-metal-on-metal THRs (n = 188). The groups had similar rates of stillbirths (0.0% vs 2.1%, p = 1.00), preterm births (25.0% vs 12.8%, p = 0.25) and LBW neonates (18.8% vs 11.7%, p = 0.42). In addition, neonates born to mothers with metal-on-metal THR were more likely to be SGA compared with those born to mothers with non-metal-on-metal THR (25.0% vs 6.9%, p = 0.03).

The proportion of elective cesarean sections (CS) was higher in the patient group than in the control group (Table 2). The overall proportion of CS was 27% before THR and 53% after THR and trial of labor more often resulted in emergency CS. The use of epidural analgesia and amniotomies were more common in the control group (Table 4).

Table 1
Background characteristics of women having singleton pregnancies ending in delivery in the patient group and in the control group.

	Patient group		Control group		
Total number	204		1417		
	n	%	n	%	P
Age at birth (years, mean SD)	33.4	5.2	32.6	5.2	0.046
Nulliparous	80	39.2	438	31.0	0.02
Previous cesarean section	37	18.1	161	11.4	0.006
Marital status					
never married	28	13.7	205	14.5	0.78
ever married	176	86.3	1212	85.5	
Maternal smoking					
non-smoker	173	84.1	1191	84.1	0.63
quit during 1st trimester	4	2.0	43	3.0	
Smoker	25	12.3	142	10.0	
unknown	2	1.0	41	2.9	
Rheumatoid arthritis	86	42.2	6	0.4	<0.001

Table 2
Perinatal characteristics and outcome in the patient group after THR and the control group.

	Patient group		Control group		
Total number	204		1417		
	n	%	n	%	p
Intended mode of delivery					
Elective CS	69	33.8	124	8.8	<0.001
Trial of labor	135	66.2	1293	91.2	
Fetal gender male	103	50.5	730	51.5	0.78
Birth length (cm) (mean; SD)	48.7	2.8	50.3	2.6	<0.001
Birth weight (grams) (mean; SD)	3240	670	3580	560	<0.001
LBW <2500g	25	12.3	41	2.9	<0.001
SGA	17	8.3	39	2.8	<0.001
LGA	3	1.5	57	4.0	0.04
Preterm, <37 + 0 weeks	28	13.7	65	4.6	<0.001
Perinatal mortality	4	2.0	10	0.7	0.09
Stillbirths	4	2.0	8	0.6	0.02
Neonatal deaths	0	0.0	2	0.1	0.99
1-minute Apgar score $\leq$ 6	13	6.4	73	5.2	0.47
Delivery related asphyxia	5	2.5	35	2.5	0.99
Phototherapy	19	9.3	63	4.4	0.003
Neonatal intensive-care unit	8	3.9	38	2.7	0.32
Neonatal status 7 days postpartum					
at home	169	82.8	1284	91.4	<0.001
in hospital	31	15.2	111	7.9	

THR = total hip replacement, SD = standard deviation, LBW = low birthweight, LGA = large for gestational age, SGA = small for gestational age.

Discussion

The results of this study raise concerns over adverse pregnancy outcomes, such as preterm birth, LBW, SGA and stillbirth, that were found to be more common in women after THR than in the control group without THR.

In Finland, the national stillbirth rate has been between 3–5 per 1000 births for the last 30 years [23]. The stillbirth rate of the control group, as well as the patient group before THR, was similar to national levels, but in the patient group after THR it was four to five times higher. One reason for the increased stillbirth rate might be the underlying diseases of the THR patients. Two of the four women with stillbirth in the patient group had RA. RA has been shown to increase the risk of preterm birth and SGA neonate, but not for stillbirths or perinatal mortality in large cohort studies [25–27]. However, the prevalence of RA was also high in the patient group before THR.

Some studies have described the possible effects of the ion release of metal-on-metal implants on fetal health. Chromium and cobalt have been shown to be toxic, but it is believed that the increased blood metal ion concentration remains below teratogenic levels. The placenta also prevents a large proportion of the ions from entering the fetal circulation [18,20]. Although the concentrations of metal ions may remain below teratogenic levels, the slightly elevated fetal blood metal ion level might influence the growth of the fetus and be involved in preterm births or stillbirths. Metal-on-metal implants gained popularity in Finland in the year

Table 3
Univariable and adjusted Odds ratios (OR) with 95% confidence intervals (CI) for pregnancy outcomes. Data were adjusted by the following variables: maternal age at delivery, smoking during pregnancy and maternal rheumatoid arthritis.

	Stillbirth OR (95% CI)	Preterm OR (95% CI)	SGA OR (95% CI)	LBW OR (95% CI)
Univariable	3.52 (1.05–11.81)	3.31 (2.07–5.30)	3.21 (1.78–5.79)	4.67 (2.77–7.87)
Adjusted*	2.72 (0.58–12.67)	3.58 (2.03–6.30)	2.83 (1.35–5.93)	4.79 (2.56–8.97)

LBW = low birthweight, SGA = small for gestational age.

Table 4
proportions of obstetric variables in attempted vaginal deliveries for the patient group and the control group.

	Patient group		Control group		
Total number	135		1293		
	n	%	n	%	P
Mode of delivery					
spontaneous vaginal	93	68.9	1056	82.1	<0.001
vacuum or forceps extraction	3	2.2	84	6.5	0.05
emergency cesarean section	39	28.9	150	11.6	<0.001
labor analgesia					
epidural	23	17.0	334	25.8	0.03
spinal	2	1.5	30	2.3	0.53
paracervical	18	13.3	219	16.9	0.28
amniotomy	33	24.4	516	39.9	<0.001
oxytocin augmentation	39	28.9	467	36.1	0.10
episiotomy	28	20.7	372	28.8	0.05
manual placental removal	1	0.7	15	1.2	0.66
uterine curettage	1	0.7	18	1.4	0.53

2000 and were widely used for the following 10 years. In this study, only the rate of SGA was significantly higher among metal-on-metal implants compared with non-metal-on-metal implants, but the same trend was also noted in other outcome measures. However, the number of patients with metal-on-metal THR was low in this study. Furthermore, no information on maternal metal ion levels was available.

The intended modes of delivery differed between groups. Women in the THR group had more elective CS and fewer trials of labor. One explanation for the higher rate of elective CS could be that patients with a replaced hip opt to have elective CS because of a possible fear of damaging the THR implant and negatively affecting the delivery outcome in vaginal delivery [10,13,15]. Women in the THR group already had higher CS proportions before THR compared with the control group, which might be explained by their underlying diseases. A German cohort study showed that women with chronic diseases were more likely to deliver by CS than healthy referents [23].

The trials of labor were more likely to result in acute CS compared with the control group. It remains unclear whether this finding was because of abnormalities in cardiotocography or prolonged labor as this information was not available. It is also possible that not all THR patients classified as having a trial of labor were really opting for vaginal delivery. The small percentage of epidural analgesia and amniotomies after THR may be explained by the possibility that a considerable number of parturients in that group had actually planned elective CS, but it had been converted to emergency CS for reasons such as early onset of labor. Our results differ from those of the largest previous study by Sierra et al. who observed a total of 47 deliveries after THR and suggested that the percentage of CS (35.0%) in their patient series did not differ from national levels [11]. A couple of smaller patient series also reported similar CS rates compared to national rates in their studies [28–30], while some smaller studies have reported increased rates of CS (41.1%–100%) [10,13,15]. However, none of these previous studies have had control groups without THRs.

One of the main strengths of this study is the large, nationwide study population with long study period. A further strength is that this is also the first study to compare post-operative deliveries to both preoperative deliveries and matching controls. Moreover, a register-based study design further eliminates any possible recall-bias. One of the benefits of these registers is their good coverage so that the data represents well the defined population. The register data are routinely collected using structured forms with nation-wide instructions that reduce possible reporting bias.

A long study period is one complicating factor when analyzing deliveries and neonatal outcomes. During the 20-year study period, delivery methods and neonatal care changed, as did the medications used for the treatment of RA. Moreover, there were some important missing variables in the MBR. For example, information on previous preterm deliveries or previous SGA children was not available. In addition, no information on body mass index was recorded before 2004, and the register data only had information on 1-minute Apgar-scores, since 5-minute scores only became part of the register in 2004. Also, durations of labor stages were not found in most of the cases, since they also became part of the register in 2004.

According to the findings of this study, adverse pregnancy outcome (preterm birth, LBW, SGA and stillbirth) are more common in women who have undergone THR. As a result, such women are more likely to have elective and emergency cesarean sections after THR. Further studies with combined multinational registries would be needed to confirm these novel findings.

Funding

This study was funded by the Competitive Research funds of Pirkanmaa Hospital District, Tampere, Finland, representing governmental funding of Finland

Conflict of interest statement

None of the authors have any potential conflicts of interests to declare

References

[1] Harris WH, Sledge CB. Total hip and total knee replacement. N Engl J Med 1990;323(11):725–31.
[2] Adelani MA, Keeney JA, Palisch A, Fowler SA, Clohisy JC. Has total hip arthroplasty in patients 30 years or younger improved? A systematic review. Clin Orthop 2013;471(August (8)):2595–601.
[3] Hannouche D, Devriese F, Delambre J, Zadegan F, Tourabaly I, Sedel L, et al. Ceramic-on-ceramic THA implants in patients younger than 20 years. Clin Orthop Relat Res 2016;474(February (2)):520–7.
[4] Skytta ET, Jarkko L, Antti E, Huhtala H, Ville R. Increasing incidence of hip arthroplasty for primary osteoarthritis in 30- to 59-year-old patients. Acta Orthop 2011;82(February (1)):1–5.
[5] Cnudde P, Nemes S, Bülow E, Timperley J, Malchau H, Kärrholm J, et al. Trends in hip replacements between 1999 and 2012 in Sweden. J Orthop Res 2018;36(1):432–42.
[6] Kurtz SM, Lau E, Ong K, Zhao K, Kelly M, Bozic KJ. Future young patient demand for primary and revision joint replacement: national projections from 2010 to 2030. Clin Orthop Relat Res 2009;467(10):2606–12.
[7] Boot CL, Heyligers IC, Heins KF. Pregnancy and delivery after revised total hip replacement. Orthopedics 2003;26(8):813–4.

[8] Maffulli N, Del Buono A, Denaro V. Hip artroplasty: a transient reason not to be pregnant. Surg 2012;10(December (6)):347–9.
[9] McDowell C, Lachiewicz P. Pregnancy after total hip arthroplasty. J Bone Joint Surg Am 2001;83(10):1490–4.
[10] Meldrum R, Feinberg J, Capello W, Detterline A. Clinical outcome and incidence of pregnancy after bipolar and total hip arthroplasty in young women. J Arthroplasty 2003;18(7):879–85.
[11] Sierra R, Trousdale R, Cabanela M. Pregnancy and childbirth after total hip arthroplasty. J Bone Joint Surg Br 2005;87(1):21–4.
[12] Smith M, Marcus P, Wurtz L. Orthopedic issues in pregnancy. Obstet Cynegol Surv 2008;63(2):103–11.
[13] Stea S, Bordini B, De Clerico M, Traina F, Toni A. Safety of pregnancy and delivery after total hip arthroplasty. J Womens Health 2007;16(9):1300–4.
[14] Yakici Y, Erkan D, Zuniga R, Bateman H, Salvati E, Magid S. Pregnancy outcomes following total hip arthroplasty: a preliminary study and review of literature. Orthopedics 2003;26(1):75–6.
[15] Ostensen M. Hip prostheses in women of fertile age. Consequences for sexuality and reproduction. Tidsskr Nor Laegeforen 1993;113(May (12)):1483–5.
[16] Brodner W, Grohs JG, Bancher-Todesca D, Dorotka R, Meisinger V, Gottsauner-Wolf F, et al. Does the placenta inhibit the passage of chromium and cobalt after metal-on-metal total hip arthroplasty? J Arthroplasty 2004;19(December (8 Suppl 3)):102–6.
[17] Novak CC, Hsu AR, Della Valle CJ, Skipor AK, Campbell P, Amstutz HC, et al. Metal ion levels in maternal and placental blood after metal-on-metal total hip arthroplasty. American Journal of Orthopedics (Chatham, Nj) 2014;43 (December (12)):304.
[18] Ziaee H, Daniel J, Datta AK, Blunt S, McMinn DJW. Transplacental transfer of cobalt and chromium in patients with metal-on-metal hip arthroplasty: a controlled study. J Bone Jt Surg - Br Vol 2007;89(March (3)):301–5.
[19] deSouza R, Wallace D, Costa ML, Krikler SJ. Transplacental passage of metal ions in women with hip resurfacing: no teratogenic effects observed. Hip Int 2012;22(1):96–9.
[20] Fritzsche J, Borisch C, Schaefer C. Case report: high chromium and cobalt levels in a pregnant patient with bilateral metal-on-metal hip arthroplasties. Clin Orthop Relat Res 2012;470(August (8)):2325–31.
[21] Oppermann M, Borisch C, Schaefer C. Hip arthroplasty with high chromium and cobalt blood levels–Case report of a patient followed during pregnancy and lactation period. Reprod Toxicol 2015;53(June):51–3.
[22] Rainio J, Perälä A, Pelanteri S. Hip and knee prosthesis, statistical report. National Institute of Health and Welfare; 2014.
[23] Vuori E, Gissler M. Perinatal statistics: parturients, deliveries and newborns 2015. National Institute of Health and Welfare; 2016.
[24] Saari A, Sankilampi U, Hannila M, Kiviniemi V, Kesseli K, Dunkel L. New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. Ann Med 2011;43(May (3)):235–48.
[25] Aljary H, Czuzoj-Shulman N, Spence AR, Abenhaim HA. Pregnancy outcomes in women with rheumatoid arthritis: a retrospective population-based cohort study. J Matern Fetal Neonatal Med 2018;(September (06)):1–7.
[26] Wallenius M, Salvesen KÅ, Daltveit AK, Skomsvoll JF. Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. Acta Obstet Gynecol Scand 2014;93(March (3)):302–7.
[27] Skomsvoll JF, Baste V, Østensen M, Irgens LM. Perinatal outcome in pregnancies of women with connective tissue disease and inflammatory rheumatic disease in Norway. Scand J Rheumatol 1999;28(January (6)):352–6.
[28] Lally L, Mandl LA, Huang W, Goodman SM. Pregnancy does not adversely affect postoperative pain and function in women with total hip arthroplasty. Jcr J Clin Rheumatol 2015;21(September (6)):323–5.
[29] Yazici Y, Erkan D, Zuniga R, Bateman H, Salvati EA, Magid SK. Pregnancy outcomes following total hip arthroplasty: a preliminary study and review of the literature. Orthopedics 2003;26(January (1)):75–6.
[30] Yoon HJ, Yoo JJ, Yoon KS, Koo K, Kim HJ. Alumina-on-alumina THA performed in patients younger than 30 years: a 10-year minimum followup study. Clin Orthop 2012;470(December (12)):3530–6.

PUBLICATION IV

Congenital anomalies in the offspring of women with total hip replacement – a nationwide register study in Finland

Kuitunen Ilari, Eskelinen Antti, Skyttä Eerik, Huhtala Heini, Artama Miia

ACCEPTED FOR PUBLICATION

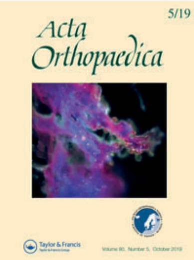
Only in printed version

PUBLICATION
V

No effect of delivery on total hip replacement survival: a nationwide register study in Finland

Kuitunen Ilari, Skyttä Eerik, Artma Miia, Huhtala Heini, Eskelinen Antti.

Acta Orthop. 2019 Oct;90(5):433-438. doi: 10.1080/17453674.2019.1628561. Epub 2019 Jun 21.



Acta Orthopaedica

ISSN: 1745-3674 (Print) 1745-3682 (Online) Journal homepage: https://www.tandfonline.com/loi/iort20

No effect of delivery on total hip replacement survival: a nationwide register study in Finland

Ilari Kuitunen, Eerik T Skyttä, Miia Artama, Heini Huhtala & Antti Eskelinen

OPEN ACCESS

Acta Orthopaedica 2019; 90 (5): 433–438

No effect of delivery on total hip replacement survival: a nationwide register study in Finland

Ilari KUITUNEN [1], Eerik T SKYTTÄ [2], Miia ARTAMA [3,4], Heini HUHTALA [3], and Antti ESKELINEN [2]

[1] Faculty of Medicine and Health Technologies, Tampere University, Tampere; [2] Coxa Hospital for Joint Replacement, and Faculty of Medicine and Health Technologies; [3] Faculty of Social Sciences, Tampere University, Tampere; [4] National Institute of Health and Welfare, Tampere, Finland
Correspondence: ilari.kuitunen@tuni.fi
Submitted 2019-03-29. Accepted 2019-05-21

Background and purpose — Previous small studies have suggested that delivery does not adversely affect the survivorship of total hip replacement (THR). We investigated whether delivery after primary THR affects hip implant survivorship in a large population-based study sample

Patients and methods — In this register-based nationwide cohort study, all women aged 15–45 who underwent primary THR in Finland from 1987 to 2007 were included from the Finnish Arthroplasty Register. Data on deliveries were obtained from the medical birth register. After primary THR, 111 women (133 THRs) delivered and formed the delivery group. In the reference group, 1,878 women (2,343 THRs) had no deliveries. We used Kaplan–Meier analysis with 95% confidence intervals (CI) to study implant survivorship at 6 and 13 years, and Cox multiple regression to assess survival and hazard ratios (HRs), with revision for any reason as an endpoint with adjustment for age, rheumatoid arthritis, and stem and cup fixation.

Results — 51 (38%) revisions were recorded in the delivery group and 645 (28%) revisions in the reference group. The 6-year implant survivorship was 91% (CI 85–96) in the delivery group and 88% (CI 87–90) in the reference group. The 13-year survival rates were 50% (CI 39–62) and 61% (CI 59–64). The adjusted HR for revision after delivery was 0.7 (CI 0.4–1.2) in ≤ 6.8 years' follow-up and 1.1 (CI 0.8–1.6) in > 6.8 years' follow-up.

Interpretation — Based on the findings in this nationwide study of hip replacement in fertile-aged women, delivery does not seem to decrease THR implant survivorship; women should not be afraid of or avoid becoming pregnant after THR.

The most common indications for THR in very young patients aged under 30 years are rheumatoid arthritis (RA), avascular necrosis of the femoral head, and developmental dysplasia of the hip (Adelani et al. 2013). The incidence of primary THR among young patients (30 to 59 years old) has increased annually in Finland from 9.5 per 100,000 person years in 1980 to 61 per 100,000 in 2007 (Skyttä et al. 2011). In 2017, over 1,000 women aged under 55 underwent a primary THR operation in Finland (open access statistical report of the Finnish Arthroplasty Register 2018: National Institute of Health and Welfare 2018).

Only a few studies with rather small sample sizes and local data have analyzed the effects of delivery and THR on each other. None of these studies have reported problems with deliveries after THR, and they indicate that THR does not majorly affect the mode of delivery (Monaghan et al. 1987, Boot et al. 2003, Meldrum et al. 2003, Yazici et al. 2003, Sierra et al. 2005, Stea et al. 2007, Smith et al. 2008) Further, THR survival is not decreased, and the delivery method does not affect THR survival (Meldrum et al. 2003, Sierra et al. 2005). However, women have reported concerns regarding vaginal delivery and fear of delivery positions harming the THR (Ostensen 1993, Meldrum et al. 2003, Stea et al. 2007).

Very young patients seem to have worse clinical outcomes in terms of pain relief and function after THR, even though implant survival rates and radiological outcomes have improved (Adelani et al. 2013, Swarup et al. 2017). Clinical outcomes may be limited by systemic diseases, such as RA, that still comprise the majority of indications for THR in these very young patients. The survivorship of the THR is often shortened due to the loosening of cup or stem in very young patients, men, and patients with a higher BMI (Melloh et al. 2011). While in some studies underlying diseases have not negatively affected the survival of the hip prosthesis (Hannouche et al. 2016), dysplastic hips appear to have worse sur-

DOI 10.1080/17453674.2019.1628561

vival rates compared with non-dysplastic hips (Tsukanaka et al. 2016). Metal-on-metal (MoM) implants have worse survival rates compared with non-MoM implants and are since 2012 are no longer used in Finland due to common adverse local tissue reactions that have led to numerous revisions (Smith et al. 2012, Furnes et al. 2014, Varnum et al. 2015). Because THR implant survival is substantially lower in very young patients compared with older patients, THR should be considered as the treatment option of last resort for very young patients (Swarup et al. 2015, Hannouche et al. 2016).

We evaluated whether delivery adversely affects the survivorship of THR in a nationwide register-based study sample.

Patients and methods

Data for this nationwide register-based study were gathered from 3 different national registers. Information on all women aged 15 to 45 who underwent THR operation in Finland between 1987 and 2007 was obtained from the Finnish Arthroplasty Register (FAR). The register is maintained by the National Institute for Health and Welfare (THL), and it contains information on all orthopedic prostheses operated from 1980 in Finland. All the information in the FAR has been collected prospectively. The current (2017) completeness of the register is 95% for primary THR, and it matches well with data from the Finnish Hospital Discharge Register (open access statistical report of the Finnish Arthroplasty Register 2018: NIHW 2018).

In the present study, the operation day of the primary THR was used as the starting point of the follow-up. Because we did not have information on primary THR operations before 1987, a revision THR as the first event in the FAR after January 1, 1987 was an exclusion criterion in the study. Women with bilateral prostheses were included, as earlier research has shown that this does not bias the results (Lie et al. 2004, Ranstam and Robertsson 2010). The endpoint for the follow-up was either revision, death, emigration, or December 31, 2007, whichever came first. The outcome was the revision of the hip for any reason.

2,012 women with 2,499 primary THRs were selected from the register. Of the THRs selected, 23 were excluded due to a lack of information on many key variables (Figure 1).

Information on pregnancies and deliveries was gathered from the National Medical Birth Register (MBR) maintained by the THL. Pregnancies and deliveries from January 1, 1987 to December 31, 2007 were included in this study. The MBR contains information on all pregnancies of at least 22 gestational weeks ending in delivery and information on deliveries and newborns. MBR data match well with hospital discharge data and the coverage of the register has improved over the years. If there was no information in the MBR, the woman was not considered to have been pregnant. In the study, women who had given birth after THR formed the delivery group, and women without pregnancy after THR formed the reference group.

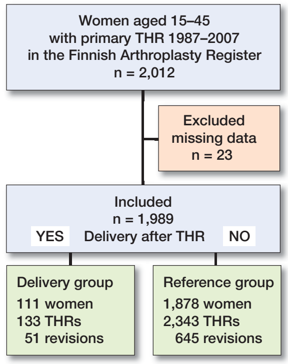


Figure 1. Flow chart of study population and events of total hip replacement (THR) survival among fertile-aged (15 to 45) women having delivery compared with women not having delivery after THR.

The Register for Reimbursable Diseases is maintained by the Finnish Social Insurance Institution of Finland. It contains information on reimbursable chronic diseases. A medical statement written by a certified doctor is needed to gain reimbursement for chronic disease. Information on all the reimbursements for this study population was obtained. If there was no information available, women were considered as not having chronic diseases.

In this study, RA was the most common diagnosis. Other chronic diseases were rare, but the following diseases were found: asthma, diabetes mellitus type 1, epilepsy, hypothyroidism, hypertension, inflammatory bowel disease, and major psychiatric disease.

Statistics

Categorized variables were compared by chi-square test between the groups and reported as proportions. Continuous variables were compared by their distribution. Normally distributed variables were compared by Student's t-test and reported by means with standard deviations (SD). Non-normally distributed variables were compared by Mann–Whitney U-test and reported by medians with interquartile range. A p-value under 0.05 was considered statistically significant in all analyses. Kaplan-Meier survival analyses with 95% confidence intervals (CI) were performed to evaluate the survival of the hips in both the delivery group and the reference group. Survival rates were calculated for 6 years' and 13 years' follow-up. The follow-up was continued until 13 years when 20 THRs were still at risk (life table analysis) in the delivery group. The follow-up period was calculated from primary THR until revision THR or until the date the patient was censored at the end of the study (December 31, 2007), or date of emigration, or date of death. The Cox proportional hazards model was used to analyze the effect of potential confounders and count hazard ratios (HR). The adjustments

Table 1. Background characteristics of the study population, types of hip prosthesis, and indications for revisions between the delivery group and the reference group. Values are frequency (%) unless otherwise specified

Factor	Delivery group n = 133	Reference group n = 2,343
Age at primary THR [a]	29 (8)	40 (8)
Follow-up period (years) [a]	9.1 (6)	8.0 (8)
Rheumatoid arthritis	62 (47)	774 (33)
Other chronic disease [b]	5 (4)	208 (9)
Nulliparous at primary THR	78 (64)	778 (33)
Indication for THR		
Inflammatory arthritis (RA + others)	62 (47)	731 (31)
Primary osteoarthritis	12 (9)	532 (23)
Secondary arthrosis	21 (16)	363 (16)
DDH [c]	22 (17)	493 (21)
Other	16 (12)	224 (10)
Metal-on-metal bearing	16 (12)	390 (17)
Type of primary THR fixation		
Uncemented	114 (86)	1,859 (79)
Hybrid	7 (5)	237 (10)
Inverse hybrid	0 (0)	1 (0)
Cemented	12 (9)	245 (10)
Revisions	51 (38)	645 (28)
Revision indications		
Aseptic loosening	30 (59)	318 (50)
Deep infection	1 (2)	11 (2)
Periprosthetic fracture	0 (0)	12 (2)
Dislocation	1 (2)	30 (5)
Others	14 (27)	193 (30)
Missing	5 (10)	81 (12)

[a] Median and interquartiles.
[b] Includes: asthma, diabetes mellitus type 1, epilepsy, hypothyroidism, hypertension, inflammatory bowel disease, major psychiatric disease.
[c] DDH = developmental dysplasia of the hip.

Table 2. Comparison of primary diagnoses and revision indications in the delivery group between women with at least 1 vaginal delivery after total hip replacement (THR) with women with only Cesarean sections after THR

Factor	Vaginal delivery after THR n = 53	Cesarean section after THR n = 80
Indication for THR		
Inflammatory arthritis (RA + others)	19	43
Primary osteoarthritis	4	8
Secondary arthrosis	13	8
DDH	10	12
Other	7	9
Revisions	15	36
Revision indications:		
Aseptic loosening	10	20
Deep infection	1	0
Dislocation	0	1
Others	4	10
Missing	0	5

DDH = developmental dysplasia of the hip.

used in the Cox proportional analysis were the following: age at the time of primary THR, RA, stem fixation, and cup fixation. Because the proportional hazards assumption was not met in the Cox model (crossing survival curves at 6.8 years), the follow-up was divided into 2 time periods, and a piecewise Cox proportional model was performed. The first follow-up period was the time before the crossing at 6.8 years, and the second period was from the crossing until the end of the follow-up (6.8–21.0 years). All the analyses were performed using SPSS statistical software version 25.0 (IBM Corp, Armonk, NY, USA).

Ethics, registration, funding, and potential conflicts of interest

In accordance with Finnish regulations, informed patient consent was not required as the women were not contacted. Our study protocol went through the ethical evaluation of the National Institute for Health and Welfare to gain access to register data, permission number: THL/599/5.05.00/2010. This study was funded by the Competitive Research funds of Pirkanmaa Hospital District, Tampere, Finland, representing governmental funding. The authors have no potential conflicts of interests to declare.

Results

1,989 women with 2,476 THRs were included in the study (Table 1). Of these, 111 (5.6%) women with 133 (5.4%) THRs had a delivery during the follow-up. The mean follow-up in the delivery group was 9.3 years (0–21), and the median age at the start of the follow-up was 29 years. In the reference group, 1,878 women with 2,343 THRs had no deliveries. The mean follow-up was 8.1 years (0–21), and the median age at the start of the follow-up was 40.

RA was the most common indication for THR in both groups. It was, however, more prevalent in the delivery group (47%) than in the reference group (33%) (p = 0.001). Other chronic diseases were more common in the reference group. The distribution of THR fixation method or bearing type was similar between the groups. The delivery group had 51 revisions, and 30 (59%) of the revisions were performed due to aseptic loosening. In the reference group, 645 THRs were revised, and 318 (49%) revisions were performed due to aseptic loosening.

The deliveries were analyzed and recorded per THR. 170 deliveries occurred during the follow-up (mean of 1.3 deliveries per THR). The maximum number of deliveries per patient during the follow-up was 5. Of the deliveries, 75 (44%) were vaginal and 95 (56%) Cesarean sections. 50 women with 53 THRs had at least 1 vaginal delivery after THR and 61 women with 80 THRs had only Cesarean sections after THR. The primary THR diagnoses and revision indications were similar in the vaginal delivery group and Cesarean section group (Table 2).

At 6 years, the survival rate in the delivery group was 91% (CI 85–96) and in the reference group 88% (CI 87–90). At 13

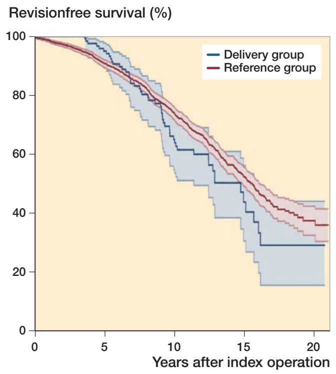


Figure 2. Kaplan–Meier survival curves (with 95% confidence intervals) of primary total hip replacement (THR) among fertile-aged women aged 15 to 45 years at the time of THR having 1 or more deliveries after THR (delivery group) compared with no deliveries after THR (reference group).

years, the survival rate was 50% (CI 39–62) for the delivery group and 61% (CI 59–64) for the reference group, respectively (Figure 2, Table 3).

During the first time period (0 to 6.8 years' follow-up), the adjusted Cox regression model showed no statistically significant difference in the risk for revision between the delivery and the reference groups (adjusted HR 0.7, CI 0.4–1.2). During the later follow-up (6.8 to 21 years), there was still no difference in adjusted HR between the groups (HR 1.1, CI 0.8–1.6).

Discussion

To our knowledge, our study is the first to assess THR implant survivorship in fertile-aged women in a large population-based study sample. Based on our results, delivery does not seem to adversely affect hip implant survivorship after primary THR.

Our results are in concordance with previous smaller studies. In their study, Sierra et al. (2005) reported that delivery after primary THR does not decrease the survival rate of the implant. They had the largest number of participants prior to our study. 343 women with 420 THR were contacted and 47 of those had pregnancy ending in delivery. However, the survival rates for 5-, 10- and 15-year follow-up periods were calculated for the whole cohort with no comparisons made between the delivery and non-delivery groups. Our 6-year survival rate in both groups was in line with these results. Meldrum et al. (2003) had 13 hips with deliveries in their study population and reported no adverse effects for THR. Yazici et al. (2003) reported 21 THR patients with deliveries and no decrease in the survival rate of the THR. All these studies were retrospective with alternative response rates (30–75%). McDowell and Lachiewicz (2001) reported 5 women with 7 uncemented

Table 3. Kaplan–Meier 6- and 13-year survival rates with 95% confidence intervals (CI) of primary total hip replacement of fertile-aged women aged 15 to 45 years at the time of THR

			K–M survivorship at 6 years		K–M survivorship at 13 years	
Delivery	No. of hips	No. of revisions	No. at risk	survival % (CI)	No. at risk	survival % (CI)
Yes	133	51	100	91 (85–96)	22	50 (39–62)
No	2,343	645	1,411	88 (87–90)	456	62 (59–64)

THRs having deliveries and, compared with matched referents, no differences between survival or hip functions were reported. Our study was the only one to report a slight but not statistically significant decrease in implant survival rate in the Kaplan–Meier analysis after delivery.

Cesarean section (CS) rate was markedly increased in the delivery group compared with overall CS rate in Finland. There have been previous reports in which women with dysplastic hips have been discussed to have smaller pelvic diameters and therefore could tend to have CS (Sierra et al. 2005; Stea et al. 2007). Developmental dysplasia of the hip was an equally common indication for THR in women who only had Cesarean sections after THR as in those who delivered vaginally after THR in our study. Also, revision indications did not differ between them. The reason for the very high CS rate in the delivery group remains unknown. We can only speculate that the presence of THR may have affected the patients' and/or the physicians' choice of delivery. However, it did not have any effect on THR survival rates.

Age was the only statistically significant variable that negatively affected THR implant survivorship. The delivery group's median age at the start of the follow-up was 29 years compared with the reference group's 40 years. Previously, only Sierra et al. (2005) have applied the Cox regression model to analyze implant survivorship after delivery. In their model, delivery seemed to decrease THR survivorship, but once age at the time of primary THR was taken as part of the model, no further differences between the delivery group and the reference group were obtained. Previous non-delivery-related THR survival studies have reported similar findings of weaker implant survivorship in younger patients (Dorr et al. 1994, Nam et al. 2016, Tsukanaka et al. 2016). In particular, very young patients under 30 years have been reported to have had decreased THR survivorship (Mohaddes et al. 2019) probably because of higher activity levels (Dorr et al. 1994, Adelani et al. 2013). Our survival rates were slightly lower compared with the recent study of Mohaddes et al. (2019), in which the 15-year THR survival rate for patients aged under 30 at the time of THR was 76%.

In young patients (< 50 years or less), indications for THR differ in comparison with older patients (+50 years). In younger patients, inflammatory arthritis and developmental hip diseases are more common, and primary osteoarthritis is rare (Adelani et al. 2013). Developmental dysplasia of the hip decreases the survival of the hip prosthesis in young patients (Havelin et al. 2000, Tsukanaka et al. 2016). There have been controversial results regarding the survival of the THR in RA patients. Some studies have suggested decreased THR survivorship, more common radiographic findings indicating implant failure, poorer function, and increased mortality among patients with RA (Creighton et al. 1998, Havelin et al. 2000, Tang and Chiu 2001, Singh and Lewallen 2013, Goodman et al. 2014, Schrama et al. 2015). Inflammatory arthritis as primary diagnosis for THR may also increase revisions due to deep infections (Dale et al. 2012). Previous large national cohort studies, however, have shown no decrease in THR survival due to RA (Havelin et al. 2000 , Furnes et al. 2001, Eskelinen et al. 2006). Because of the high prevalence of RA among young patients, it was taken as part of the Cox model. In our model, RA did not decrease THR survival. Indeed, it seemed patients with RA had better results during the first follow-up period (< 6.8 years). A similar finding was seen in a previous THR and delivery study, where Serra et al. (2005) found no decrease in the survival of hips operated due to an RA diagnosis in their step-by-step Cox results.

The main strength of our study is the register-based design. Previous THR survival studies after delivery have been retrospective cohorts with questionnaires. Our design eliminates possible recall bias and has better completeness because revision indications are also reported to the Finnish Arthroplasty Register. In addition, we had by far the largest study population with the longest follow-up, and our results are nationwide instead of from one hospital district catchment area. In addition, we were also able to combine information from several nationwide registers on patients' long-term diseases and pregnancies.

The first limitation of our study is the lack of patient-reported outcome measurements (PROMs), which forced our study to focus strictly on the survival of the implant. However, absence of PROM data does not affect our interpretation of the survival results. The second limitation was the study period. Our study period was from 1987 to 2007. Even though the implants used today differ greatly from those implanted 30 years ago, contemporary implant designs were used in the latter half of the study period, and this approach also enabled us to assess long-term implant survivorship in this rare cohort of patients.

In conclusion, based on the findings in this nationwide study offering hip replacement to fertile females, delivery does not seem to decrease THR implant survivorship. Women should not be afraid of or avoid becoming pregnant after THR.

IK, MA, ES, HH, and AE had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MA, ES, and AE contributed to the conception and design of the study. IK drafted the manuscript. AE supervised the study. HH, IK, and AE were responsible for the statistical analyses. All authors participated in the interpretation of data and in the critical revision of the manuscript.

The authors would like to thank Mr. Peter Heath for language editing of the manuscript.

Acta thanks Anne Garland and Maziar Mohaddes for help with peer review of this study.

Adelani M A, Keeney J A, Palisch A, Fowler S A, Clohisy J C. Has total hip arthroplasty in patients 30 years or younger improved? A systematic review. Clin Orthop 2013; 471(8): 2595-601.

Boot C L, Heyligers I C, Heins K F. Pregnancy and delivery after revised total hip replacement. Orthopedics 2003; 26(8): 813-14.

Creighton M G, Callaghan J J, Olejniczak J P, Johnston R C. Total hip arthroplasty with cement in patients who have rheumatoid arthritis: a minimum ten-year follow-up study. J Bone Joint Surg Am 1998; 80(10): 1439-46.

Dale H, Fenstad A M, Hallan G, Havelin L I, Furnes O, Overgaard S, et al. Increasing risk of prosthetic joint infection after total hip arthroplasty. Acta Orthop 2012; 83(5): 449-58.

Dorr L D, Kane T J, Conaty J P. Long-term results of cemented total hip arthroplasty in patients 45 years old or younger: a 16-year follow-up study. J Arthroplasty 1994; 9(5): 453-6.

Eskelinen A, Paavolainen P, Helenius I, Pulkkinen P, Remes V. Total hip arthroplasty for rheumatoid arthritis in younger patients: 2,557 replacements in the Finnish Arthroplasty Register followed for 0–24 years. Acta Orthop 2006; 77(6): 853-65.

Furnes O, Lie S A, Espehaug B, Vollset S E, Engesaeter L B, Havelin L I. Hip disease and the prognosis of total hip replacements: a review of 53,698 primary total hip replacements reported to the Norwegian Arthroplasty Register 1987–99. J Bone Joint Surg Br 2001; 83(4): 579-86.

Furnes O, Paxton E, Cafri G, Graves S, Bordini B, Comfort T, Rivas M C, Banerjee S, Sedrakyan A. Distributed analysis of hip implants using six national and regional registries: comparing metal-on-metal with metal-on-highly cross-linked polyethylene bearings in cementless total hip arthroplasty in young patients. J Bone Joint Surg Am 2014; 96 Suppl 1: 25-33.

Goodman S M, Ramsden-Stein D N, Huang W, Zhu R, Figgie M P, Alexiades M M, et al. Patients with rheumatoid arthritis are more likely to have pain and poor function after total hip replacements than patients with osteoarthritis. J Rheumatol 2014; 41(9): 1774-80.

Hannouche D, Devriese F, Delambre J, Zadegan F, Tourabaly I, Sedel L, et al. Ceramic-on-ceramic THA implants in patients younger than 20 years. Clin Orthop Relat Res 2016; 474(2): 520-7.

Havelin L I, Engesaeter L B, Espehaug B, Furnes O, Lie S A, Vollset S E. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. Acta Orthop Scand 2000; 71(4): 337-53.

Lie S A, Engesaeter L B, Havelin L I, Gjessing H K, Vollset S E. Dependency issues in survival analyses of 55,782 primary hip replacements from 47,355 patients. Stat Med 2004; 23(20): 3227-40.

McDowell C, Lachiewicz P. Pregnancy after total hip arthroplasty. J Bone Joint Surg Am 2001; 83(10): 1490-4.

Meldrum R, Feinberg J, Capello W, Detterline A. Clinical outcome and incidence of pregnancy after bipolar and total hip arthroplasty in young women. J Arthroplasty 2003; 18(7): 879-85.

Melloh M, Eggli S, Busato A, Roder C. Predictors of early stem loosening after total hip arthroplasty: a case-control study. J Orthop Surg 2011; 19(3): 269-73.

Mohaddes M, NaucléR E, Kärrholm J, Malchau H, Odin D, Rolfson O. Implant survival and patient-reported outcome following total hip arthroplasty in patients 30 years or younger: a matched cohort study of 1,008 patients in the Swedish Hip Arthroplasty Register. Acta Orthop 2019; 90(3): 249-52.

Monaghan J, Lenehan P, Stronge J, Gallagher J. Pregnancy and vaginal delivery following bilateral hip replacement. Eur J Obstet Gynecol Reprod Biol 1987; 26(3): 261-4.

Nam D, Nunley R M, Berend M E, Berend K R, Lombardi A V, Barrack R L. Residual symptoms and function in young, active hip arthroplasty patients: comparable to normative controls? J Arthroplasty 2016; 31(7): 1492-7.

National Institute of Health and Welfare. Open access statistical report of the Finnish Arthroplasty Register. 2018. Available at http:www.thl.fi/far.

Ostensen M. [Hip prostheses in women of fertile age: consequences for sexuality and reproduction]. Tidsskr Nor Laegeforen 1993; 113(12): 1483-5.

Ranstam J, Robertsson O. Statistical analysis of arthroplasty register data. Acta Orthop 2010; 81(1): 10-14.

Schrama J C, Fenstad A M, Dale H, Havelin L, Hallan G, Overgaard S, et al. Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements. Acta Orthop 2015; 86(4): 469-76.

Sierra R, Trousdale R, Cabanela M. Pregnancy and childbirth after total hip arthroplasty. J Bone Joint Surg Br 2005; 87(1): 21-4.

Singh J A, Lewallen D G. Patients with osteoarthritis and avascular necrosis have better functional outcomes and those with avascular necrosis worse pain outcomes compared to rheumatoid arthritis after primary hip arthroplasty: a cohort study. BMC Med 2013; 11: 210.

Skyttä E T, Leskinen J, Eskelinen A, Huhtala H, Remes V. Increasing incidence of hip arthroplasty for primary osteoarthritis in 30- to 59-year-old patients. Acta Orthop 2011; 82(1): 1-5.

Smith M, Marcus P, Wurtz L. Orthopedic issues in pregnancy. Obstet Cynegol Surv 2008; 63(2): 103-11.

Smith A J, Dieppe P, Vernon K, Porter M, Blom A W; National Joint Registry of England and Wales. Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet 2012; 379(9822): 1199-204.

Stea S, Bordini B, De Clerico M, Traina F, Toni A. Safety of pregnancy and delivery after total hip arthroplasty. J Women's Health 2007; 16(9): 1300-4.

Swarup I, Lee Y, Christoph E I, Mandl L A, Goodman S M, Figgie M P. Implant survival and patient-reported outcomes after total hip arthroplasty in young patients with juvenile idiopathic arthritis. J Arthroplasty 2015; 30(3): 398-402.

Swarup I, Shields M, Mayer E N, Hendow C J, Burket J C, Figgie M P. Outcomes after total hip arthroplasty in young patients with osteonecrosis of the hip. Hip Int 2017; 27(3): 286-92.

Tang W M, Chiu K Y. Primary total hip arthroplasty in patients with rheumatoid arthritis. Int Orthop 2001; 25(1): 13-16.

Tsukanaka M, Halvorsen V, Nordsletten L, Engesaeter I O, Engesaeter L B, Marie Fenstad A, et al. Implant survival and radiographic outcome of total hip replacement in patients less than 20 years old. Acta Orthop 2016; 87(5): 479-84.

Varnum C, Pedersen A B, Mäkelä K, Eskelinen A, Havelin L I, Furnes O, Kärrholm J, Garellick G, Overgaard S. Increased risk of revision of cementless stemmed total hip arthroplasty with metal-on-metal bearings. Acta Orthop 2015; 86(4): 491-7.

Yazici Y, Erkan D, Zuniga R, Bateman H, Salvati E A, Magid S K. Pregnancy outcomes following total hip arthroplasty: a preliminary study and review of the literature. Orthopedics 2003; 26(1): 75-6.