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Congenital anomalies in the offspring of women with total hip replacement: a nationwide register study in Finland

Short title: Congenital anomalies in the offspring of women with total hip replacement

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17 Abstract

18 Background

19 Few previous studies have analysed the possible teratogenic effect of maternal total hip
20 replacement (THR) on congenital anomalies. The aim of this study was to estimate the risk of
21 major congenital anomalies in the offspring of women with THR. Furthermore, we compared the
22 risks based on type of implant (metal-on-metal (MoM)/Non-MoM).

23 Methods

24 The study population for this register-based cohort study was gathered from six Finnish national
25 registers. All fertile-aged females who underwent THR from 1980 to 2007 and three reference
26 females for each THR patient without THR were selected. THR operation day was the start of
the 27 follow-up for both groups. Information on pregnancies, induced abortions (IA) and
congenital 28 anomalies was gathered for the years 1987-2007 and the proportions of congenital
anomalies 29 were compared.

30 Results

31 In the THR group, 2 429 women had 256 pregnancies, 205 (80.1%) deliveries and 51 (19.9%) IAs. In
32 the reference group, 7 276 women had 1 670 pregnancies, 1 443 (86.4%) deliveries and 236
33 (13.6%) IAs. There was no difference in the incidence of major anomalies between the THR (3.5%,
34 n=9) and the reference group (3.6%, n=60), p=0.91. In the THR group, there was no difference in
35 the risk of major anomalies between the patients with a MoM-THR (10.5%, 2/19) and those with a
36 non-MoM (2.9%, 7/241) (OR 3.93, 95% Confidence interval 0.76-20.2; p=0.13).

37 Conclusions

38 Reassuringly, maternal THR does not appear to increase the risk of major congenital anomalies or

pregnancies ending due to suspected foetal anomalies. Further studies with larger study populations are needed to further assess the risk of anomalies in the offspring of women having MoM-THR.

Introduction

Total hip replacement (THR) is a highly effective operation that results in major improvements in the quality of life of patients (1-4). Moreover, THR has become one of the most common surgeries performed in Finland (5). Indeed, the incidence of primary THR in younger patients aged 30 to 59 years old increased from 9.5 per 100 000 person years in 1980 to 61 per 100 000 person years in 2007. The increase in incidence was smaller in the youngest age group (30-39) compared with the older age groups (40-49 and 50-59) (6). During the same period, the total annual number of primary THRs performed on women aged less than 55 years increased from 238 to 468 (7).

In 2017, over 1 000 women aged under 55 underwent THR in Finland (7). In young patients (under 30 years old), the most common indications for THR are juvenile rheumatoid arthritis (RA), avascular necrosis of the femoral head and developmental dysplasia of the hip (8).

Previous studies have shown that pregnancy and delivery are safe after THR. These studies have, however, been relatively small local case series. Although it seems THR does not have an effect on the choice of delivery method nor on neonatal health (9-19), fertility rates are lower after THR (20), and some women with THR may still have concerns about becoming pregnant (16).

MoM implants, used in Finland from 2000 to 2012, release Cr and Co which may cause locally adverse reactions to metal debris and elevated blood Cr and Co levels (21, 22). In animal studies, Cr has been shown to be toxic for the foetus and to cause malformations (23, 24). In addition, Co has genotoxic effects (25-27). The ions released from MoM-THR also have the potential to cause chromosomal damage to human cells (28, 29). Indeed, one case report describes a woman with MoM THR and elevated serum chromium (Cr) and cobalt (Co) levels who

had a newborn with a congenital anomaly (hypospadias) (30). Furthermore, during pregnancy, high maternal Cr levels increase the risk of preterm birth (31).

The placenta has been shown to reduce Cr and Co blood concentrations even though the ion levels remain higher compared with references without elevated maternal Cr and Co levels (32-34). In a retrospective case series, women with a MoM hip resurfacing implant were reported to have undergone 17 pregnancies with 14 newborns without any anomalies detected (35). Another study reported three healthy newborns without malformations when the mother had a MoM hip replacement and also elevated Co and Cr ion levels (36). In a recent case report, the authors described one healthy newborn with increased umbilical cord Cr and Co levels at birth that normalised during the first three months, and no harm to the newborn was detected (37).

The aim of this present study was to evaluate the risk of major congenital anomalies in the offspring of women who had undergone THR compared with a reference group without THR. Further, we also evaluated whether MoM-THR would increase the risk compared with non-MoM-THR and a reference group without THR.

Materials and Methods

In this register-based nationwide cohort study, the study population was gathered from six different Finnish national registers. All the fertile-aged (15-45 years old) females who had undergone THR surgery from 1980 to 2007 were identified from the Finnish Arthroplasty Register (FAR), maintained by the National Institute for Health and Welfare. The register was established in 1980, and the completeness of the register is high for primary THR, being 95% in 2017 (7).

For every THR patient, three reference persons without recorded THR were selected from the Finnish Population Information System maintained by the Population Register Centre. These referents were matched by age, mother tongue and current place of residence. The start for the follow-up was the THR operation day in the THR patient group and the same day was used for the matched referents.

Information on pregnancies was obtained from three different registers, all maintained by National Institute of Health and Welfare. The Medical Birth Register includes information on pregnancies ending in birth after gestational week 22 or births weighing at least 500 grams and deliveries and birth health outcomes up to seven days postpartum. The Medical Birth Register was established in 1987 and information on all pregnancies from 1987 to 2007 was gathered for this study. The Register on Induced Abortions (IA) has information on legally terminated pregnancies that are performed in hospitals. It contains maternal background characteristics and abortion indications. The register was established in 1983, but information on national IA ratios is available from 1950.

The Register of Congenital Anomalies was established in 1962. In this study, we obtained all the congenital anomalies from 1987 to 2007 for both study groups. The register contains information on diagnosed or suspected major and minor anomalies in newborns and foetuses. Every year, more than 2 000 major anomalies are reported to the register. In this study, we evaluated all the anomalies and confirmed the major/minor diagnoses and then categorised the diagnoses. Anomalies were grouped according to the ICD-10 classification.

Information on RA was obtained from the register of medical reimbursements maintained by Social Insurance Institution of Finland. To gain reimbursement for medical costs due to chronic

disease, a certificate by a certified doctor is required. Participants without a record of RA reimbursement were considered as not having the disease.

Permissions

All the data were linked by using the individual personal identification code. No written consent was needed since the participants were not contacted. Permission to use the data was granted by the register holders. Permission number: THL/599/5.05.00/2010.

Statistics

This study was based on partly prospectively collected nationwide register data. We then conducted a retrospective analysis of this data. Means with standard deviations (SD´s) were calculated for Gaussian populations and medians with interquartile ranges for Non-Gaussian populations. Categorised variables were analysed by Chi-square test or Fischer's exact test. A P-value under 0.05 was considered to be statistically significant. Odds ratios with 95% Confidence intervals (CI) were calculated to compare congenital anomalies between groups and subgroups. Statistical analyses were performed by using the IBM SPSS for Windows v25.0- statistical program.

Results

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 19.9% (n=51) in IA. In the reference group, 7 276 women had 1 670 pregnancies, and 86.4% of which (n=1 434) ended in delivery and 13.6 %

(n=236) in IA, p=0.02. 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%) newborns had one or more major anomaly. In the THR patient group, 3 (5.9%) of the 51 IAs were performed due to suspected foetal 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. 47 (3.3%) of the newborns had one or more major anomaly. In this group, 13 (5.5%) of the 236 IAs were performed due to suspected foetal defects, and all of them had at least one major anomaly recorded to the register. No major differences between these group were observed. When comparing RA patients and non-RA patients between the THR patient and reference group, no differences were found. Background characteristics and comparison between the groups are presented in Table I.

In the subgroup analysis, women who had undergone MoM-THR had 19 births/foetuses 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 (2.9 %, 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).

In the THR patient group, 9 newborns and foetuses with major anomalies had 25 anomaly diagnoses, and in the reference group 60 newborns and foetuses with major anomalies had 143 anomaly diagnoses. The most common major anomalies were heart and circulatory organ anomalies, ICD-10 codes Q20 – Q28 (5 newborns/foetuses 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 II)

Discussion

We found 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 and patients might have concerns towards pregnancy after THR, these findings could possibly serve to decrease these concerns (16, 20).

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, the true effect remains uncertain. MoM implants have been shown to release metal ions (Cr and Co) into the blood circulation that may be harmful to human cells (21, 22, 28). Even though the placenta prevents the majority of ions from entering the foetal blood circulation, the ion levels in the foetuses of MOM-THR patients have been shown to be elevated compared with foetuses without maternal MoM-THR (32-34). 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. (35) 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. Therefore further research is needed to clarify this issue. It also seems obvious that we need either longer follow-up to confirm this result or, alternatively, a study

approach, where information from several national registries would be merged to study this issue. These actions could potentially solve this problem.

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, newborns 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 to 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 (38, 39). In our study, the THR and RA patients had similar rates of congenital anomalies compared with non-RA patients.

To the best of our knowledge, this is the first register-based study that assesses the effect of THR on the incidence of congenital anomalies on a population-based level and with a reference group. Our study provides nationwide data with a long study period and follow-up. The data recorded to the registers have good quality and completeness. Moreover, the register-based study design eliminates recall bias since the anomalies were gathered from recorded reliable registers instead of questionnaires.

We acknowledge a few limitations in this study. First, the low number of events during the study period weakens the generalisability of our results. 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. Second, an even longer study follow-up would have aided us in evaluating more reliably whether the MoM-implants would potentially affect the incidence of anomalies.

Conclusions

Maternal THR does not increase the risk of congenital anomaly in newborns. 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.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with this study.

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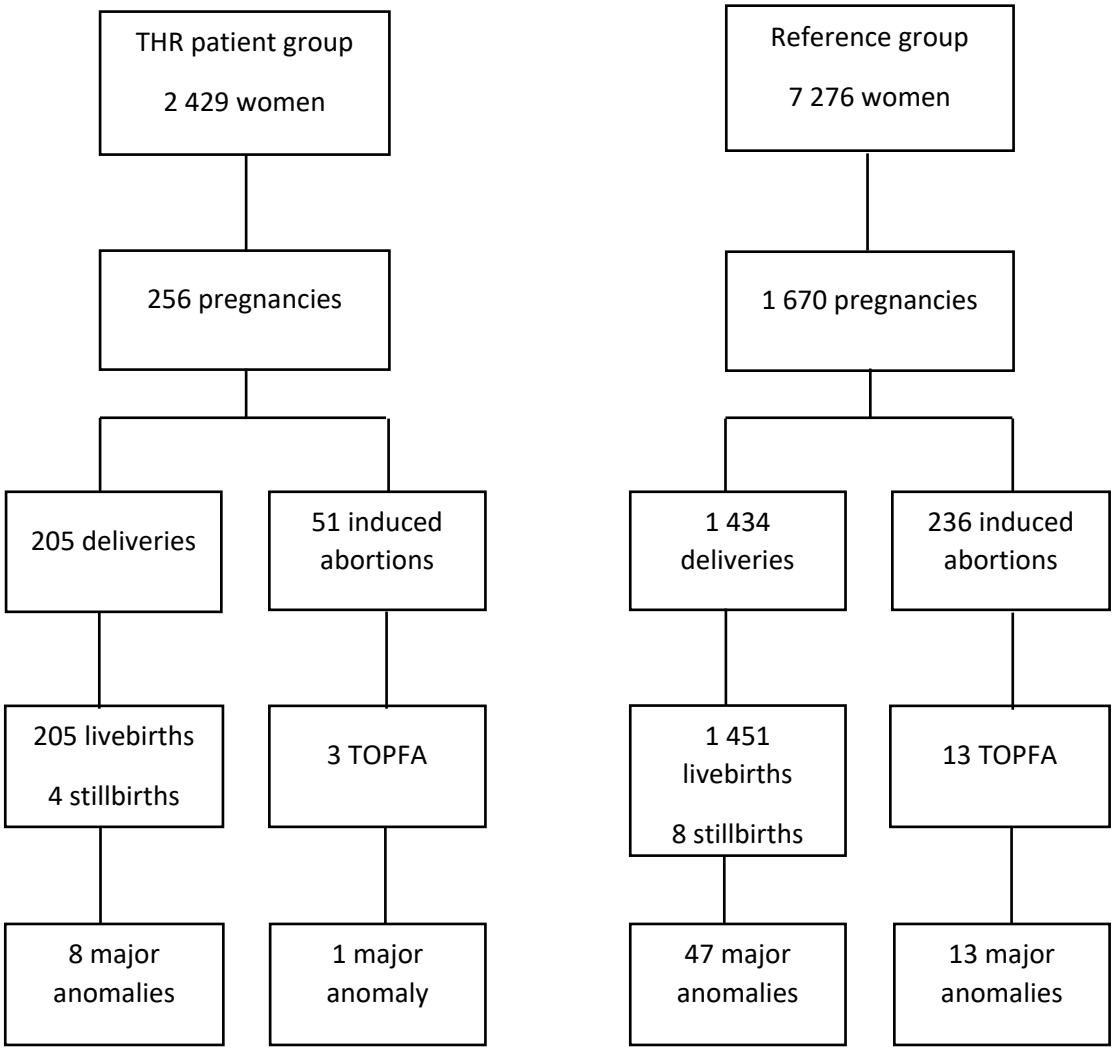
Figure I. Flow chart of study population and pregnancies in the THR patient and the reference cohort.



TOPFA = Termination of pregnancy due to foetal anomaly.

THR = Total hip replacement

Table I. Total number of births/terminated pregnancies due to foetal anomaly, number 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.

	Women with THR			Women without THR					
	Births/foetuses	Major anomalies		Births/foetuses	Major anomalies		OR	95% CI	
	n	n	%	n	N	%		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
Non-MoM	241	7	2.9						

*TOPFA = termination of pregnancy due to foetal 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.

Table II. Proportions of major congenital anomalies in births/foetuses 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	100.0	25	100.0	60	100.0	143	100.0
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