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Long-term risk of endometrial cancer after assisted reproductive technology

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ABSTRACT

STUDY QUESTION: What is the risk of endometrial cancer after long-term follow-up in women treated with ART between 1983 and 2001 compared with women in the general population and subfertile women who did not undergo ART?

SUMMARY ANSWER: The risk of endometrial cancer is not increased in women who underwent ART in the Netherlands between 1983 and 2001, neither compared with women from the general population nor compared with subfertile women not treated with ART.

WHAT IS KNOWN ALREADY: Concerns have been raised that subfertility treatment may be associated with increased risk of endometrial cancer. However, published studies show inconsistent results regarding the effects of ovarian stimulation and specific subfertility diagnoses on endometrial cancer risk.

STUDY DESIGN, SIZE, DURATION: A nationwide historic cohort study (the OMEGA-cohort) was conducted to examine the risk of cancer in women after ovarian stimulation for ART. The OMEGA-cohort comprises 30 625 women who received ovarian stimulation for ART (ART group) in 1983–2000 and 9988 subfertile women not treated with ART (non-ART group). After a median follow-up of 24 years, endometrial cancer incidence was ascertained through linkage with the Netherlands Cancer Registry. Endometrial cancer risk in the cohort was compared with that in the general population using person-years analyses, and between the ART group and non-ART group using multivariable Cox regression analyses.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Detailed ART-treatment data were obtained from the medical records and complete information on parity and age at first birth was obtained through linkage with the Personal Records Database. Information on hysterectomy and endometriosis was collected through linkage with the Dutch Nationwide Pathology Databank (Palga). Data about lifestyle factors, including BMI, were obtained through a self-administered questionnaire.

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MAIN RESULTS AND THE ROLE OF CHANCE: After a median follow-up duration of 24 years, 137 endometrial cancers were diagnosed. Endometrial cancer risk after ART was not significantly increased compared with that in the general population (standardized incidence ratio = 1.19; 95% CI = 0.97–1.44) nor compared with that in the non-ART group (multivariably adjusted hazard ratio = 1.11; 95% CI = 0.74–1.67). Risk of endometrial cancer did not increase with longer follow-up or with more ART cycles, and the risk within the cohort, did not vary by cause of subfertility (male, tubal, unexplained, and other). Irrespective of ART treatment, endometrial cancer risk was increased in obese women and women with endometriosis, but decreased among parous women and women who used oral contraceptives.

LIMITATIONS, REASONS FOR CAUTION: Although the findings of the study are reassuring, the median age of the women at the end of follow-up (median age 56 years) was still rather young. Therefore, there is a need for at least 10–15 additional follow-up years to draw definitive conclusions. In addition, other large studies are needed to investigate the risk of endometrial cancer in women who underwent ART.

WIDER IMPLICATIONS OF THE FINDINGS: The results of this study contribute to knowledge about long-term health after ART treatment, which is valuable to subfertile couples, considering or undergoing fertility treatments, and their healthcare providers.

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Introduction

Nowadays, subfertility affects 10–15% of couples in developed countries (Mascarenhas *et al.*, 2012), implying that it is a major problem in the Western world. Since the introduction of ART, such as IVF in 1978, ART has become a common procedure with more than 2 million cycles administered annually (ESHRE, 2018).

Fertility drugs used in ART treatment temporarily raise serum levels of gonadotropins and gonadal hormones, and consequently increase the chances of multiple folliculogenesis and ovulation. As a consequence, concerns have been raised that ovarian stimulation for ART may lead to a long-term increase in the risk of hormone-related cancers (Whittemore *et al.*, 1992; Brinton, 2007; Silva Idos *et al.*, 2009; Brinton *et al.*, 2012). So far, most studies have focused on the effects of ovarian stimulation for ART on the risks of breast and ovarian cancer, because these cancers are more frequent than endometrial cancer during young adulthood and middle age (Brinton *et al.*, 2012, 2013a). Yet, endometrial cancer incidence rises sharply after age 55 years and is the most common cancer of the female genital tract. Now that the first generation of ART-treated women is reaching their sixties and seventies, studies investigating the long-term effects of ART on endometrial cancer risk are of great public health importance. The few studies published so far have shown inconsistent results (Jensen *et al.*, 2009; Parazzini *et al.*, 2010; Brinton *et al.*, 2013a,b; Guleria *et al.*, 2019; Barcroft *et al.*, 2021). Moreover, low statistical power, short follow-up, and lack of controls for important confounders have limited the conclusions from these studies. Because nulliparity is an established risk factor for endometrial cancer (Henderson *et al.*, 1983; La Vecchia *et al.*, 1993; Raglan *et al.*, 2019) and hormonal subfertility diagnoses such as polycystic ovary syndrome (PCOS), ovulation disorders, and endometriosis have also been associated with endometrial cancer risk (Rotterdam, 2004; Chittenden *et al.*, 2009; Brinton *et al.*, 2010), it is crucial to account for parity as well as subfertility diagnosis when assessing the effect of ART on endometrial cancer risk (Barcroft *et al.*, 2021).

Therefore, the aim of the current study was to determine the risk of endometrial cancer after long-term follow-up in a nationwide cohort of 30 625 women who underwent ART treatment between 1983 and 2001, compared with women in the Dutch general population and with subfertile women not treated with ART.

Materials and methods

Study population

A nationwide retrospective cohort study with prospective follow-up was conducted to investigate long-term effects of ovarian stimulation for ART, covering ART treatments applied in 1983–2000. In 1995–1996, the OMEGA-I cohort was identified, comprising 19 861 women who started ovarian stimulation for ART in 1983–1994 in 1 of the 12 IVF clinics in the Netherlands (ART group) and a comparison group of 7515 women seeking fertility treatment in 1980–1994 in four clinics, but not treated with ART (non-ART group). To obtain a large enough comparison group of subfertile women not treated with ART, we identified women who were diagnosed with fertility problems shortly before ART became a routine procedure for subfertile patients. We attempted to frequency match the non-ART comparison group according to the distribution of subfertility diagnoses in the ART group. Most women in the non-ART group underwent tubal surgery, (low-dose ovarian stimulation for) IUI or hormonal treatments (e.g. clomiphene), or withdrew from the waiting list for ART. The OMEGA-I cohort and data collection methods have been extensively described (van Leeuwen *et al.*, 2011; van den Belt-Dusebout *et al.*, 2016; Spaan *et al.*, 2021).

In 2010–2012, the OMEGA-II cohort was established comprising 12 500 women who started ART treatment in 1995–2000 in the same clinics and 4863 subfertile women not treated with ART in 1980–2000 in one of the IVF clinics or two regional hospitals to expand the non-ART group (Supplementary Fig. S1). The institutional ethics committees of all 14 hospitals approved the study procedures, which have been described in detail previously (van Leeuwen *et al.*, 2011; Spaan *et al.*, 2015).

Collection of subfertility treatment data and potential confounders

For the OMEGA-I cohort, trained abstractors registered subfertility causes, fertility-improving surgical procedures, and for each IUI and ART cycle, date, dosage and type of fertility drug, and outcome from medical records. For the OMEGA-II cohort, electronic medical record data were obtained for all centers. Furthermore, 42 169 women were invited in 1997–1999 (OMEGA-I) or in 2010–2013 (OMEGA-II) to complete a risk factor questionnaire and informed consent form for future linkages with disease registries. The questionnaire ascertained information on reproductive histories, fertility treatments, hormone use, lifestyle, and family history of cancer. Of these women, 61% completed the questionnaire.

In 2013, all cohort members except women who declined linkages (94.1% of the cohort), were linked with the Personal Records Database, yielding nearly complete information on parity and age at first birth until August 2013. Information on hysterectomy and histologically proven endometriosis was collected through linkage with the Dutch Nationwide Pathology Databank (Palga).

Ascertainment of outcome data

Cancer incidence from 1989 until July 2018 was ascertained through the population-based Netherlands Cancer Registry (NCR) (Van den Brandt *et al.*, 1990; van Leeuwen *et al.*, 2011) for 94.1% of the entire cohort, i.e. excepting women who declined linkage (Van den Brandt *et al.*, 1990). Cancer diagnoses included all invasive malignancies and borderline ovarian tumors except for non-melanoma skin cancer (IARC, 2008). Information on each malignancy included date of diagnosis, topography, and morphology. The Personal Records Database provided vital status for all women.

Statistical analysis

The NCR achieved full coverage of the Netherlands in 1989. Therefore, the observation time for each participant started on 1 January 1989, date of the first ART treatment (ART group), or date of first clinic visit for subfertility evaluation (non-ART group), whichever came last. To exclude tumors diagnosed during diagnosis or treatment of subfertility, time at risk in the current analysis was calculated from 1 year after the first ART treatment/visit gynecologist until the date NCR follow-up ended (1 July 2018), date of diagnosis of any first malignancy, date of hysterectomy, or date of death, whichever came first. Women originally included in the non-ART group who subsequently received ART (n = 1144), contributed person-time to the non-ART group until the date of first ART treatment, then switched to the ART group from this date, according to standard cohort methodology regarding time-dependent allocation of person-years in case of changing exposure (Breslow and Day, 1987). Women were excluded if there was a cancer diagnosis before 1989 (start NCR) or before ART treatment or subfertility evaluation (N = 192, including one endometrial cancer).

First, endometrial cancer incidence in the cohort was compared with incidence in the general population. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed and expected numbers of tumors in the cohort. Expected numbers were based on sex-, age-, and calendar year-specific incidence rates from the NCR (IARC, 2008). Second, Cox proportional hazards models, with cumulative numbers of ART cycles and births as time-dependent variables and age (in years) as time scale, were used to compare the risks of endometrial cancer for various fertility treatments and diagnoses between the ART and non-ART groups. All other variables were included as fixed variables. None of the variables violated the proportional hazards assumption. Cumulative incidences of endometrial cancer at age 60 years were calculated within the ART and non-ART groups, separately for parous and nulliparous women, using the life-table method.

Exposure variables (ART, IUI, and fertility drug use) were primarily based on medical record data and supplemented with data from questionnaires if missing. Missing values for number of ART cycles and subfertility diagnosis were imputed using single imputation by a regression model. Information regarding potential confounding factors, such as oral contraceptive (OC) use and BMI was primarily available from the questionnaires and supplemented with information from the medical record, if available. Missing values were categorized as a separate category.

Age at the start of treatment or first gynecologist visit, number of births, age at first birth, subfertility diagnosis, endometriosis, number of IUI cycles, OC or menopausal hormone use, and BMI were tested as potential confounders. Confounders were defined as factors changing the risk estimate for the exposure of interest by 10% or more in a model including the potential confounder(s) and the variable of interest. Confounders were tested in models restricted to women who responded to the questionnaire since information on a number of potential confounders was missing for non-responders. Selected confounders were subsequently included in all analyses including both responders and non-responders.

Sensitivity analyses were performed to: (i) eliminate the potential influence of IUI on our risk estimates by exclusion of all women ever exposed to IUI, and (ii) eliminate the effect of left-censoring by exclusion of all women treated before 1989 (start NCR). Trend tests were based on the *P*-value of the category-specific mean as a continuous variable (Breslow and Day, 1987). All tests of statistical significance were two-sided; a *P*-value of <0.05 was considered statistically significant. All analyses were performed with STATA 15 (StataCorp, 2017).

Results

Population characteristics

Of the 40 613 cohort members, 30 625 were ART-treated women and 9988 were subfertile women never treated with ART (Table 1). Non-ART women had a slightly longer median follow-up duration than ART-treated women (25.3 years [interquartile range (IQR) = 21.6–29.5] vs 22.3 years [IQR = 19.8–25.9]) and consequently were slightly older at the end of follow-up (median age 55.6 [IQR = 51.9–61.7] vs 54.4 [IQR = 51.6–59.9] years). The mean number of ART cycles in the ART group was 3.3. ART-treated women more often remained nulliparous than women in the non-ART group (35.4% vs 25.2%).

Risk of endometrial cancer

In total, 137 endometrial malignancies (including sarcomas) occurred: 103 in the ART group and 34 in the non-ART group (Supplementary Table S1). Three endometrial cancers occurred in the first year of follow-up. The most frequent histologic type was endometrial carcinomas: 93% in the ART group and 91% in the non-ART group (WHO, 2020). Only a few mesenchymal

Table 1. Population characteristics by ART exposure status.

	ART group N = 30 625 No. (%)	Non-ART group N = 9988 No. (%)	Total N = 40 613 No.
Year of birth			
1955	3597 (11.8)	2245 (22.5)	5842
1955–1959	8622 (28.2)	2617 (26.2)	11 239
1960–1964	10 468 (34.2)	2759 (27.6)	13 227
≥1965	7938 (25.9)	2367 (23.7)	10 305
Subfertility diagnosis[a]			
Male factor	8205 (26.8)	1646 (16.5)	9851
Tubal factor	7896 (25.8)	2672 (26.8)	10 568
Unexplained or other factor[b]	10 147 (33.1)	2816 (28.2)	12 963
Missing	4377 (14.3)	2854 (28.6)	7231
Age at first ART treatment or first visit to the gynecologist (years), mean ± SD[c]	33.1 (4.3)	31.4 (4.9)	32.6 (4.5)
Age at first ART treatment or first visit to the gynecologist (years)[c]			
<27	2457 (8.0)	1878 (18.8)	4335
27–29	4920 (16.1)	2157 (21.6)	7077
30–32	7941 (25.9)	2295 (23.0)	10 236
33–35	7448 (24.3)	1908 (19.1)	9356
≥36	7859 (25.7)	1750 (17.5)	9609
Year of first ART treatment or first visit to the gynecologist[c]			
<1989	1818 (5.9)	3040 (30.4)	4858
1989–1992	8731 (28.5)	2977 (29.8)	11 708
1993–1996	11 633 (38.0)	2473 (24.8)	14 106
1997–2000	8443 (27.6)	1498 (15.0)	9941
Total no. of ART cycles[d]			
0	0 (0.0)	9988 (100.0)	9988
1–2	11 520 (37.6)	0 (0.0)	11 520
3–4	10 695 (34.9)	0 (0.0)	10 695
5–6	3733 (12.2)	0 (0.0)	3733
≥7	2080 (6.8)	0 (0.0)	2080
Missing	2597 (8.5)	0 (0.0)	2597
Total no. of IUI and ART cycles[d]			
0	0 (0.0)	4584 (45.9)	4584
1–2	8103 (26.5)	891 (8.9)	8994
3–4	7909 (25.8)	736 (7.4)	8645
5–6	4009 (13.1)	503 (5.0)	4512
≥7	8054 (26.3)	383 (3.8)	8437
Missing	2550 (8.3)	2891 (28.9)	5441
Time since first treatment (years)[c,e]			
<10	2624 (8.6)	620 (6.2)	3244
10–14	1595 (5.2)	485 (4.9)	2080
15–19	5785 (18.9)	1337 (13.4)	7122
20–24	11 585 (37.8)	2561 (25.6)	14 146
25–29	8015 (26.2)	2939 (29.4)	10 954
≥30	1021 (3.3)	2046 (20.5)	3067

	ART group N = 30 625 No. (%)	Non-ART group N = 9988 No. (%)	Entire cohort N = 40 613 No.
Age at the end of follow-up (years)			
<45	3497 (11.4)	1064 (10.7)	4561
45–49	3844 (12.6)	1292 (12.9)	5136
50–54	7489 (24.5)	2128 (21.3)	9617
55–59	8799 (28.7)	2483 (24.9)	11 282
≥60	6996 (22.8)	3021 (30.3)	10 017
No. of births[f]			
0	10 832 (35.4)	2517 (25.2)	13 349
1	9766 (31.9)	2486 (24.9)	12 252
≥2	9913 (32.4)	4844 (48.5)	14 757
Missing	114 (0.4)	141 (1.4)	255
Age at first birth (years)[f,g]			
<30	6390 (20.9)	3534 (35.4)	9924
30–34	7526 (24.6)	2368 (23.7)	9894
≥35	5720 (18.7)	1410 (14.1)	7130
Missing	43 (0.1)	18 (0.2)	61

(continued)

Table 1. Continued

	ART group N = 30 625 No. (%)	Non-ART group N = 9988 No. (%)	Entire cohort N = 40 613 No.
BMI			
<18.5	722 (2.4)	149 (1.5)	871
18.5–24.9	12 652 (41.3)	2791 (27.9)	15 443
25–29	4862 (15.9)	1166 (11.7)	6028
≥30	2107 (6.9)	561 (5.6)	2668
Missing	10 282 (33.6)	5321 (53.3)	15 603
Oral contraceptive use (years)			
0	3398 (11.1)	765 (7.7)	4163
1–5	5337 (17.4)	1034 (10.4)	6371
≥5	10 419 (34.0)	2162 (21.7)	12 581
Missing	11 471 (37.5)	6027 (60.3)	17 498
Hormone Replacement use			
Never	12 552 (41.0)	2255 (22.6)	14 807
Ever	671 (2.2)	215 (2.2)	886
Missing	17 402 (56.8)	7518 (75.3)	24 920

No., number.
[a] Includes the major subfertility diagnosis, based on information from medical records if available and on information from questionnaires if no medical record information was available. If several diagnoses had been registered, without mention of the main diagnosis, the following order was applied: male factor, tubal factor, unexplained, or other factor (including hormonal factor) for main diagnosis.
[b] Other factors includes factors such as endometriosis and cervical factors and hormonal factors such as ovulation disorders, polycystic ovary syndrome, and premature menopause.
[c] Indicating the age at start follow-up. First treatment indicates start of ART treatment for ART group and first visit at gynecologist' for the non-ART group.
[d] Based on information from medical records if available and on information from questionnaires if no medical record information was available.
[e] Follow-up ended at date of any first cancer diagnosis, date of hysterectomy, date of death, date of completeness of cancer registry (1 July 2018), or date of questionnaire completion for OMEGA-I women who declined linkage with the Netherlands Cancer Registry (n = 1091), whichever came first. Cancer diagnoses included all invasive malignancies except for non-melanoma skin cancer, according to the International Agency for Research on Cancer Classification (IARC, 2008).
[f] Based on the Personal Records Database and questionnaires. Includes all births up till August 2013.
[g] Only among 27 009 parous women (19 679 ART and 7330 non-ART).

tumors occurred, including six sarcomas (5.8%) in the ART group and three (8.8%) in the non-ART group. Median age at diagnosis of endometrial cancer was 53.6 years.

Comparisons with external reference rates

In the entire cohort, the risk of endometrial cancer (including sarcomas) was not significantly increased compared with risk in the general population (SIR = 1.11; 95% CI = 0.96–1.37, excluding the first year of follow-up). The SIRs of endometrial cancer were also not significantly increased in the ART group (SIR = 1.19; 95% CI = 0.97–1.44) nor in the non-ART group (SIR = 0.93; 95% CI = 0.64–1.31, *P*-difference = 0.21), when compared with the general population (Table 2). Risk of uterine sarcoma was also not increased, neither in the ART group (SIR = 0.70; 95% CI = 0.26–1.53; n = 6) nor in the non-ART group (SIR = 0.97; 95% CI = 0.20–2.84; n = 3). Endometrial cancer risk compared to the general population did not change with an increasing number of ART cycles (*P*-trend = 0.38) nor with longer follow-up (*P*-trend = 0.94), with a SIR of 1.06 (95% CI = 0.76–1.46) for ART-treated women followed for more than 20 years. ART-treated women with endometriosis were at an increased risk of endometrial cancer (SIR = 1.79; 95% CI = 1.00–2.96) compared with women in the general population.

While nulliparous ART-treated women had an increased risk of endometrial cancer compared to the general population (SIR = 1.88; 95% CI = 1.45–2.40), risk decreased with increasing number of births (≥2 births, SIR = 0.54; 95% CI = 0.29–0.92, *P*-trend < 0.001).

Comparisons within the cohort

Among parous women, the cumulative incidences of endometrial cancer at age 60 years were 0.29% for the ART group and 0.35% for the non-ART group (*P*-value 0.67). Among nulliparous women, the cumulative incidences of endometrial cancer at age 60 years were 0.90% for the ART group and 0.76% for the non-ART group (*P*-value 0.30). The age-adjusted hazard ratio (HR) of endometrial cancer (including sarcomas) associated with ART compared with no ART was 1.22 (95% CI = 0.82–1.81). When adjusted for number of births and age at start of ART treatment or subfertility evaluation, the HR was 1.11 (95% CI = 0.74–1.67). None of the other included covariates changed the estimates for the association between ART exposure and endometrial cancer risk. Risk of endometrial cancer did not increase with more ART cycles and did not vary by subfertility diagnosis (male, tubal, unexplained, or other, including hormonal; Table 3). In sensitivity analysis excluding women ever exposed to IUI, the relative risk of endometrial cancer was also comparable (HR = 1.09, 95% CI = 0.61–1.95).

Histologically proven endometriosis was associated with an increased risk of endometrial cancer (HR = 1.69; 95% CI = 1.03–2.78), adjusted for ART use and number of births. Clomiphene use in ART-treated women was not significantly associated with risk of endometrial cancer compared with no clomiphene use (HR = 1.30, 95% CI = 0.74–2.28).

Irrespective of ART exposure, risk significantly decreased with an increasing number of births (≥2 births HR = 0.34, 95% CI = 0.21–0.54) and longer duration of OC use (≥6 years HR = 0.30, 95% CI = 0.17–0.52). Obese women (BMI ≥30) were at significantly increased risk compared to women with a normal BMI (18.5–24.9) (HR = 4.04; 95% CI = 2.44–6.69) (Table 3). In stratified analyses, the HRs for endometrial cancer associated with ART treatment were not significantly increased in subgroups according to follow-up duration (HR for ≥20 years = 0.93, 95% CI = 0.55–1.60), attained age (HR for ≤55 years = 1.52, 95% CI = 0.83–2.79; HR for >55 years = 0.78, 95% CI = 0.44–1.39), parity (HR for nulliparous = 1.51, 95% CI = 0.83–2.77; HR for parous = 0.87, 95% CI = 0.50–1.52), or any other risk factor (Table 4).

Discussion

To the best of our knowledge, our nationwide study is the first one assessing long-term endometrial cancer risk after ART

Table 2. Incidence of endometrial cancer compared with the general population, excluding the first year of follow-up.[a]

	ART				Non-ART			
	Person-years	Observed/Expected[b]	SIR (95% CI)	P-value[c]	Person-years	Observed/Expected[b]	SIR (95% CI)	P-value[c]
Entire cohort	886 847	134/120.5	1.11 (0.96–1.37)					
ART exposure								
Non-ART	NA	NA	NA		237 344	33/35.4	0.93 (0.64–1.31)	
ART	649 502	101/85.1	1.19 (0.97–1.44)	0.21	NA	NA	NA	NA
Number of ART cycles[d,e]								
1–2	258 695	40/32.4	1.23 (0.88–1.68)					
3–4	246 195	42/32.2	1.31 (0.94–1.77)		NA	NA	NA	NA
≥5	144 616	19/20.5	0.93 (0.56–1.44)	0.42				
				P-trend = 0.38				
Age at first ART cycle or first visit to the gynecologist (years)								
<30	158 734	15/8.7	1.73 (0.97–2.85)		99 311	8/8.2	0.98 (0.42–1.93)	
30–32	170 193	18/16.3	1.10 (0.65–1.74)		54 389	7/7.5	0.93 (0.37–1.92)	
33–35	157 944	26/22.6	1.16 (0.75–1.69)		44 444	7/8.5	0.83 (0.33–1.70)	
≥36	162 631	42/37.6	1.12 (0.81–1.51)	0.54	39 200	11/11.3	0.97 (0.49–1.74)	0.99
				P-trend = 0.30				
Time since first ART cycle or first visit to the gynecologist (years)[e,f]								
1–14	411 046	24/22.4	1.07 (0.69–1.59)					
15–19	215 477	38/26.1	1.46 (1.03–2.00)		175 658	11/13.4	0.82 (0.41–1.47)	
≥20	22 434	39/36.6	1.06 (0.76–1.46)	0.44	61 375	22/22.0	1.00 (0.63–1.51)	0.59
				P-trend = 0.94				
Parity[g]								
Nulliparous	228 789	64/34.1	1.88 (1.45–2.40)		60 348	13/10.7	1.22 (0.65–2.08)	
1 birth	204 480	24/26.4	0.91 (0.58–1.35)		57 940	9/8.6	1.05 (0.48–1.99)	
≥2 births	213 622	13/24.2	0.54 (0.29–0.92)	<0.001	150 151	11/15.5	0.71 (0.35–1.27)	0.40
				P-trend < 0.001				
Subfertility diagnosis[e,h]								
Male factor	196 678	28/22.2	1.26 (0.84–1.82)		53 887	8/6.2	1.28 (0.55–2.52)	
Tubal factor	200 570	29/29.5	0.98 (0.66–1.41)		90 545	9/16.5	0.54 (0.25–1.03)	
Unexplained or other factor	252 255	44/33.5	1.32 (0.96–1.77)	0.44	92 913	16/12.7	1.27 (0.72–2.05)	0.07
OHSS[e]								
Never	628 849	98/83.0	1.18 (0.96–1.44)		NA	NA	NA	NA
ever	20 653	3/2.2	1.38 (0.28–4.03)	0.80				
BMI[i]								
<25	287 256	35/38.2	0.92 (0.64–1.27)		105 756	8/10.3	0.77 (0.33–1.52)	
25.0–29.9	101 973	19/12.8	1.49 (0.90–2.33)		27 484	4/3.8	1.06 (0.29–2.71)	
≥30	43 914	18/5.2	3.49 (2.07–5.51)		13 409	6/1.7	3.59 (1.32–7.82)	
Missing	216 359	29/29.0	1.00 (0.67–1.44)	<0.001	126 532	15/19.6	0.76 (0.43–1.26)	
				P-trend < 0.001				
Endometriosis[j]								
No	583 466	86/76.8	1.12 (0.90–1.38)		222 177	30/33.2	0.91 (0.61–1.29)	
Yes	66 036	15/8.4	1.79 (1.00–2.96)	0.11	15 168	3/22.8	1.32 (0.27–3.85)	

SIR, standardized incidence ratio; OHSS, ovarian hyperstimulation syndrome.
[a] Women with endometrial cancer diagnosed as a first malignancy.
[b] Expected numbers of endometrial cancer were calculated by multiplying sex-, 5-year age-, and 1-year calendar-specific population incidence rates from the Netherlands Cancer Registry with the corresponding number of person-years observed among OMEGA cohort members.
[c] P-value of likelihood ratio test.
[d] Based on information from medical records if available and on information from questionnaires if no medical record information was available. Missing values were imputed using single imputation. Total number of ART cycles by end of follow-up (fixed variable).
[e] Among 30 577 ART-treated women only; 101 endometrial cancers, excluding the first year of follow-up.
[f] Follow-up ended at date of any first cancer diagnosis, date of hysterectomy, date of death, date of completeness of cancer registry (1 July 2018), or date of questionnaire completion for OMEGA-I women who declined linkage with the Netherlands Cancer Registry (n = 1091), whichever came first. Cancer diagnoses included all invasive malignancies except for non-melanoma skin cancer, according to the International Agency for Research on Cancer Classification (IARC, 2008). All women were allocated to the correct follow-up interval according to the start of first ART or first visit to the gynecologist, even when time at risk started from 1989 onward, whereas ART or first visit to the gynecologist was before 1989.
[g] Parity status by end of follow-up (fixed variable). Based on the Personal Records Database and questionnaires. Includes all births up till August 2013. Two hundred fifty-four women with unknown parity status including one woman with endometrial cancer were excluded.
[h] Includes the major subfertility diagnosis, based on information from medical records if available and on information from questionnaires if no medical record information was available. If several diagnoses had been registered, without mention of the main diagnosis, the following order was applied: male factor, tubal factor, unexplained, or other factor (including hormonal factor) for main diagnosis.
[i] Based on information from questionnaires. BMI at date of questionnaire completion (fixed variable).
[j] Histologically proven, based on information from the Dutch Nationwide Pathology Databank (Palga).

treatment, comparing with the general population as well as a subfertile group. Additionally, we were able to adjust for the effects of other risk factors for endometrial cancer, including parity, age at first birth, age at start, subfertility diagnosis, endometriosis, number of IUI cycles, OC or menopausal hormone use, and BMI. After a median follow-up of 24 years, ART was not associated with an increased risk of endometrial cancer, neither when compared with the general population nor when compared with subfertile women not treated with ART. Moreover, risks did not increase with more ART cycles or after longer follow-up.

Table 3. Endometrial cancer risk according to fertility treatment characteristics and lifestyle risk factors, excluding the first year of follow-up.

	No. of endometrial cancers	No. of women	Crude HR (95% CI)[a]	Adj. HR (95% CI)[a]
ART exposure				
Non-ART	33	9975	1 [Reference]	1 [Reference]
ART	101	30 577	1.22 (0.82–1.81)	1.11 (0.74–1.67)
Total no. of ART cycles[b]				
0	33	9975	1 [Reference]	1 [Reference]
1–2	40	12 494	1.25 (0.78–1.99)	1.24 (0.77–1.99)
3–4	42	11 589	1.34 (0.85–2.13)	1.16 (0.72–1.86)
≥5	19	6494	0.97 (0.55–1.70)	0.85 (0.48–1.51)
Total no. of ART and IUI cycles[b]				
0	17	4577	1 [Reference]	1 [Reference]
1–2	24	9055	1.03 (0.55–1.96)	1.01 (0.54–1.92)
3–4	30	8690	1.29 (0.71–2.36)	1.13 (0.61–2.09)
5–6	18	4515	1.47 (0.75–2.88)	1.30 (0.66–2.56)
≥7	25	8447	1.02 (0.55–1.90)	0.91 (0.48–1.70)
Missing	20	5268	1.04 (0.54–1.99)	0.97 (0.51–1.87)
Response at first ART cycle[c,d]				
Normal response	44	14 950	1 [Reference]	1 [Reference]
Poor response	20	4341	1.19 (0.70–2.02)	1.05 (0.62–1.79)
Missing	37	11 286	1.17 (0.75–1.81)	1.13 (0.73–1.76)
OHSS[c,e]				
No	98	29 613	1 [Reference]	1 [Reference]
Yes	3	964	1.13 (0.36–3.56)	1.30 (0.41–4.13)
Subfertility diagnosis[f,g]				
Male factor	35	11 574	1 [Reference]	1 [Reference]
Tubal factor	37	12 962	0.70 (0.44–1.11)	0.72 (0.45–1.15)
Unexplained or other factor	62	16 016	1.10 (0.73–1.67)	1.11 (0.74–1.69)
Subfertility diagnosis Omega-I[f,g]				
Male factor	18	4863	1 [Reference]	1 [Reference]
Tubal factor	25	7068	0.74 (0.40–1.36)	0.77 (0.42–1.42)
Hormonal factor	27	4132	1.52 (0.84–2.76)	1.56 (0.86–2.84)
Unexplained or other factor	15	4005	0.93 (0.47–1.85)	0.92 (0.46–1.83)
Clomiphene use[c,g]				
Never	23	9717	1 [Reference]	1 [Reference]
Ever	27	6515	1.35 (0.77–2.36)	1.30 (0.74–2.28)
Missing	51	14 345	1.20 (0.73–1.97)	1.14 (0.70–1.88)
Endometriosis[g,h]				
No	116	36 944	1 [Reference]	1 [Reference]
Yes	18	3608	1.84 (1.12–3.03)	1.69 (1.03–2.78)
Endometriosis[g,i]				
No	105	33 702	1 [Reference]	1 [Reference]
Yes	29	6850	1.45 (0.96–2.19)	1.36 (0.90–2.05)
Parity, number of births[g]				
Nulliparous	77	13 307	1 [Reference]	1 [Reference]
Parous, 1 birth	33	12 237	0.52 (0.35–0.79)	0.52 (0.34–0.78)
Parous, 2 or more births	24	14 754	0.35 (0.22–0.55)	0.34 (0.21–0.54)
BMI[g,j,k]				
18.5–24.9	41	15 426	1 [Reference]	1 [Reference]
<18.5	2	870	0.87 (0.21–3.59)	0.89 (0.21–3.67)
25–29.9	23	6024	1.60 (0.96–2.66)	1.64 (0.99–2.74)
≥30	24	2663	4.02 (2.43–6.65)	4.04 (2.44–6.69)
Missing	44	15 569	1.03 (0.67–1.58)	1.00 (0.66–1.54)
Menopausal hormone use[g,j,l]				
No	62	14 791	1 [Reference]	1 [Reference]
Yes	6	881	1.33 (0.57–3.09)	1.21 (0.52–2.83)
Missing	2	195	2.44 (0.60–9.97)	2.25 (0.55–9.23)
Oral contraceptive use[g,j,m]				
None	30	4160	1 [Reference]	1 [Reference]
1–5 years	30	6366	0.69 (0.41–1.14)	0.69 (0.42–1.15)
6 or more years	23	12 564	0.29 (0.17–0.50)	0.30 (0.17–0.52)
Missing	51	17 462	0.42 (0.27–0.66)	0.42 (0.27–0.66)

Adj., adjusted; HR, hazard ratio; No., number; OHSS, ovarian hyperstimulation syndrome.

[a] Cox regression analyses: models using age (in years) as time scale. Number of ART cycles and number of births are included as time-dependent variables, all other variables are included as fixed variables. All adjusted analyses are adjusted for number of births and age at start. The first year of follow-up and consequently, three endometrial cancers are excluded.

[b] Based on information from medical records if available and on information from questionnaires if no medical record information was available. Missing values were imputed using single imputation.

[c] Among 30 577 ART-treated women only; 101 endometrial cancers, excluding the first year of follow-up.

[d] Poor response includes canceled first cycles because of anticipated poor response and less than four oocytes; normal response includes four or more oocytes collected in first cycle;.

[e] OHSS includes women who had had no ovum pick-up because of (anticipated) OHSS.

[f] Includes the major subfertility diagnosis, based on information from medical records if available and on information from questionnaires if no medical record information was available. If several diagnoses had been registered, without mention of the main diagnosis, the following order was applied: male factor, tubal factor, unexplained, or other factor (including hormonal factor) for main diagnosis.

[g] Additionally adjusted for ART exposure (yes/no).

[h] Histologically proven, based on information from the Dutch Nationwide Pathology Databank (Palga).

[i] Any endometriosis, based on information from Palga, medical records, and questionnaires.

[j] Analyzed within 15 935 responding women (13 417 ART and 2518 non-ART) only, with time at risk starting at date of questionnaire completion, because this information is only available from the questionnaires.

[k] BMI at date of questionnaire completion.

[l] Ever use of menopausal hormones until date of questionnaire completion.

[m] Total life-time duration until date of questionnaire completion.

Table 4. Endometrial cancer risk for ART versus non-ART treatment within risk factor subgroups.[a,b]

Endometrial cancer risk factors	ART group		Non-ART group		
	No. of Endo-metrial cancers	No. of women	No. of Endo-metrial cancers	No. of women	Adjusted HR for ART vs non-ART (95% CI)
Age at first ART treatment or first visit to the gynecologist (years)					
<32	28	12 610	13	5600	1.24 (0.64–2.41)
≥32	73	17 967	20	4375	1.03 (0.62–1.72)
Time since first ART treatment or first visit to the gynecologist (years)[c]					
<10	7	29 920	5	9460	0.12 (0.01–1.01)
10–19	53	27 978	6	9357	2.21 (0.95–5.15)
≥20	41	20 595	22	7527	0.93 (0.55–1.60)
Attained age (years)[d]					
≤55	64	30 577	13	9974	1.52 (0.83–2.79)
>55	37	15 774	20	5496	0.78 (0.44–1.39)
Subfertility diagnosis[e]					
Male	28	9353	7	2221	1.04 (0.45–2.39)
Tubal	28	9152	9	3810	1.59 (0.74–3.42)
Unexplained or other factor	45	12 072	17	3944	0.91 (0.52–1.60)
Parity[f]					
Nulliparous	64	10, 797	13	2510	1.51 (0.83–2.77)
Parous	37	19 667	20	7324	0.87 (0.50–1.52)
Endometriosis[g]					
No	86	27 590	30	9354	1.10 (0.72–1.70)
Yes	15	2987	3	621	1.26 (0.36–4.38)
BMI[h]					
18.5–24.9	35	13 358	8	2938	1.03 (0.48–2.24)
25–29.9	19	4860	4	1164	1.27 (0.43–3.76)
≥30	18	2103	6	560	0.91 (0.36–2.30)

No., number; HR, hazard ratio.
[a] Cox regression analyses: models with age (in years) as time scale.
[b] Not all numbers add up to 100%, because of missing values.
[c] First treatment indicates start of ART treatment for ART group and first visit at gynecologist' for the non-ART group.
[d] Analyses for attained age ≤55 years comprise all person-years of women until their 56st birthday or date of any first cancer diagnosis, date of hysterectomy, date of death, date of completeness of cancer registry (1 July 2018), or date of questionnaire completion for OMEGA-I women who declined linkage with the Netherlands Cancer Registry (n = 1091), whichever came first. Analyses for attained age >55 years comprise only person-years of women who were older than age 55 years at the end of follow-up, starting at their 56st birthday, until date of any first cancer diagnosis, date of hysterectomy, date of death, date of completeness of cancer registry (1 July 2018), or date of questionnaire completion for women who declined linkage with the Netherlands Cancer Registry, whichever came first. Cancer diagnoses included all invasive malignancies except for non-melanoma skin cancer, according to the International Agency for Research on Cancer classification (IARC, 2008).
[e] Includes the major subfertility diagnosis, based on information from medical records if available and on information from questionnaires if no medical record information was available. Hormonal factors include ovulation disorders, polycystic ovary syndrome, and premature menopause; non-hormonal factors include male factor, tubal factor, unexplained, and other factors such as endometriosis and cervical factors. If several diagnoses had been registered, without mentioning of the main diagnosis, the following order was applied: male factor, tubal factor, hormonal factor, other factor, or unexplained for main diagnosis.
[f] Based on the Personal Records Database and questionnaires. Includes all births up till August 2013.
[g] Histologically proven, based on information from the Dutch Nationwide Pathology Databank (Palga).
[h] Analyzed within 15 935 responding women (13 417 ART and 2518 non-ART) only, with time at risk starting at date of questionnaire completion, because this information is only available from the questionnaires. BMI at date of questionnaire completion.

Independent of ART, endometrial cancer risk was about 4-fold higher in obese women and 1.7-fold higher in women with endometriosis, but risk decreased with increasing parity and longer durations of OC use.

While several studies have examined the association between fertility treatment and the risk of endometrial cancer, only a few have specifically included ART-treated women. The largest study to date on endometrial cancer risk after ART, published by Williams *et al.* (2018), included all women who had ART in Great Britain between 1991 and 2011 (n = 255 786), with a relatively short mean follow-up duration of 8.8 years. Based on 164 endometrial cancers in their cohort, the risk of endometrial cancer was not increased compared with that in the general population (SIR = 1.12; 95% CI = 0.95–1.30). However, this study did not include a subfertile comparison group and could not account for differences in reproductive characteristics between ART-treated women and the general population.

Three meta-analyses were also inconclusive with regard to long-term endometrial cancer risk after ART treatment (Siristatidis *et al.*, 2013; Skalkidou *et al.*, 2017; Barcroft *et al.*, 2021). Skalkidou *et al.* concluded that there is a need for register-based studies with long-term follow-up, with fertility treatment details and adjustment for confounding factors, to unravel the effects of ART treatment and subfertility causes. They stated that detailed analyses concerning histologic types, dose–response effects, and the potentially modifying roles of parity, gravidity, or age at first exposure are warranted.

The only large study which has compared endometrial cancer risk after fertility treatment with risk in an untreated subfertile comparison group, included 83 endometrial cancers among 54 362 Danish infertile women treated between 1965 and 1998 (Jensen *et al.*, 2009). The median follow-up duration was 16.0 years and the median age at the end of follow-up was 47 years. Ever use of any fertility drug was not associated with uterine cancer risk (rate ratio = 1.10, 95% CI = 0.69–1.76, adjusted for number of births). However, the risk of endometrial cancer was 2.2-fold significantly increased after gonadotropin use, specifically after follicle-stimulating hormone and human menopausal gonadotropin, primarily after 10 years of follow-up, and also 2-fold increased after more than six cycles of clomiphene or

human chorionic gonadotrophin (Jensen *et al.*, 2009). The authors concluded that gonadotropins, and possibly clomiphene and human chorionic gonadotrophin, may increase the risk of endometrial cancer, with higher doses and longer follow-up leading to greater risk. A limitation of this study is that it was not known whether drugs were administered in the framework of ART, IUI, or neither of these. Another limitation of the Danish study is the lack of information on important confounders, such as BMI, subfertility diagnosis, and OC and menopausal hormone use.

Some causes of subfertility have been associated with increased risk of endometrial cancer, but the results have been rather inconsistent. Three- to nine-fold increased risks of endometrial cancer have been reported in women with PCOS and other hormonal subfertility diagnoses (e.g. ovulation disorders, endometriosis, and unexplained subfertility) (Rotterdam, 2004; Chittenden *et al.*, 2009; Brinton *et al.*, 2010; Mogensen *et al.*, 2016). However, PCOS is present in ∼18% of subfertile women (Teede *et al.*, 2018), implying that numbers of endometrial cancers after a PCOS diagnosis are small in most studies, including our own; therefore the true risk of endometrial cancer among PCOS women remains unclear (Chittenden *et al.*, 2009; Silva Idos *et al.*, 2009; Brinton *et al.*, 2010). Moreover, the association with PCOS may have been overestimated, because PCOS occurs more often in obese women, who have an increased risk of endometrial cancer (Barry *et al.*, 2014). In our study, the absence of an association between ART and risk of endometrial cancer could not be explained by differences in PCOS prevalence between our ART and non-ART groups.

We observed that histologically proven endometriosis (based on Palga data) was associated with a 1.7-fold significantly increased risk of endometrial cancer, adjusted for age at start of ART or subfertility evaluation and number of births. For endometriosis based on combined information from Palga, the medical records, and women's questionnaires, the risk was not increased, probably because, in that analysis, milder types of (not histologically proven) endometriosis were also included. Recent studies, however, reported no increased risk of endometrial cancer in women with endometriosis (Saavalainen *et al.*, 2018; Li *et al.*, 2019; Kvaskoff *et al.*, 2021).

Clomiphene might influence the development of prognostically unfavorable endometrial cancers because of its structural similarity to tamoxifen, which has been associated with a higher frequency of non-endometrioid tumors, especially serous adenocarcinomas and carcinosarcomas (Bergman *et al.*, 2000; Hoogendoorn *et al.*, 2008). In the current study, clomiphene use in ART-treated women was not significantly associated with risk of endometrial cancer compared with no clomiphene use (HR = 1.3, adjusted for number of births). Furthermore, the proportions of endometrioid and non-endometrioid tumors in our study were comparable with that in the Dutch general female population, arguing against a tamoxifen-like effect of clomiphene on endometrial cancer pathogenesis (Venn *et al.*, 2001). A few previous studies have examined the effect of fertility drugs such as clomiphene and gonadotropins on endometrial cancer risk without mentioning whether these drugs were administered for ART treatment (Reigstad *et al.*, 2017; Guleria *et al.*, 2021). Whereas a population-based Norwegian study found elevated risk of endometrial cancer for clomiphene exposure compared with no clomiphene exposure in nulliparous women (HR = 4.49; 95% CI = 2.66–7.60), but not for parous women (HR = 1.52; 95% CI = 0.67–3.42) (Reigstad *et al.*, 2017), a larger Danish study among 146 104 subfertile women did not find increased endometrial cancer risk after clomiphene use, neither among nulliparous women (HR = 1.00; 95% CI = 0.60–1.65) nor among parous women (HR = 0.84; 95% CI = 0.49–1.43) (Guleria *et al.*, 2021).

Risk factors for endometrial cancer known from studies in the general population were also identified in our subfertile cohort. Endometrial cancer risk was increased in women who remained nulliparous compared with parous women, adjusted for ART treatment. Obesity and endometriosis were associated with increased risk of endometrial cancer whereas OC use decreased the risk. None of these factors changed the estimate of the association between ART treatment and risk of endometrial cancer.

Strengths of the current study include the long-term and complete follow-up regarding endometrial cancer and vital status, the availability of a subfertile comparison group in addition to population-based reference data, detailed fertility treatment data, complete information on hysterectomy and endometriosis, and near complete information on important confounders such as number of births and subfertility diagnosis. A subfertile comparison group is crucial because ART-treated women differ from the general population regarding several risk factors for endometrial cancer (e.g. nulliparity, age at first birth, and endometriosis). We also had information on potential confounders, such as BMI, exogenous hormone use, and endometriosis. We had the unique opportunity to combine data from different sources, i.e. registries, medical records, and self-reported data, which enabled collection of complete and high-quality data by selecting the most optimal source for each variable. The ascertainment of endometrial cancer in the entire cohort (including non-responders to the questionnaire and deceased individuals) through the NCR eliminated selection bias and misclassification bias that could have resulted if we had relied on self-reported diagnoses.

Despite our long follow-up (median, 24 years), the OMEGA cohort is still relatively young (median attained age, 56 years) to draw definitive conclusions about endometrial cancer risk, as the incidence rises steeply after the age of 55–60 years (IARC, 2008). Consequently, the number of endometrial cancers was especially small in subgroups.

Several potential confounding factors, such as BMI, had high rates of missing data because these were based on questionnaire data (response rate 61%). However, near complete information was available on the most important potential confounding factors age and parity. Furthermore, adjustment for BMI, OC, and menopausal hormone use, did not affect our risk estimates.

To examine whether left-censoring affected our results, we performed an analysis restricted to women who entered the cohort after 1988. These results (based on fewer events and shorter follow-up) were quite similar overall, with an HR of 1.08 (95% CI = 0.67–1.77) for the association between ART and endometrial cancer.

In conclusion, in the first 30 years after treatment, ART does not appear to be associated with an increased risk of endometrial cancer. Although these findings are reassuring, it must be considered that the median age of the women at the end of follow-up was still rather young. Therefore, there is a need for at least 10–15 additional follow-up years. In addition, more and larger studies (i.e. by international pooling) are necessary to draw definitive conclusions.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals in the study. The data will be shared on reasonable request to the corresponding author.

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Authors' roles

F.E.v.L, Ma.S., and A.W.vd.B.-D 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. Study concept and design: F.E. v.L., C.W.B., A.W.vd.B.-D, Ma.S., H.v.B. Acquisition, analysis, or interpretation of data: C.B.L., F.J.M.B., J.S.E.L., E.J.P.v.S., L.A.J.v.d. W., B.J.C., A.W.N., J.M.J.S., A.E.P.C., M.G., R.J.T.v.G., M.M.v.R., L.L. v.L., P.A.M.M., J.P.d.B, G.M.O., M.A.G., H.v.B., A.W.vd.B.-D, F.E.v.L, Ma.S., C.W.B. Drafting of the manuscript: Ma.S., A.W.vd.B.-D, F.E. v.L. Critical revision of the manuscript for important intellectual content: C.W.B., C.B.L., Mi.S., F.J.M.B., J.S.E.L., E.J.P.v.S., L.A.J.v.d. W., B.J.C., A.W.N., J.M.J.S., A.E.P.C., M.G., R.J.T.v.G., M.M.v.R., L.L. v.L., P.A.M.M., J.P.d.B., G.M.O., M.A.G. Statistical analysis: Ma.S., A.W.vd.B.-D, F.E.v.L, Mi.S. Funding: F.E.v.L. and C.W.B. Administrative, technical, or material support: A.W.vd.B.-D, F.E. v.L, Ma.S. Study supervision: F.E.v.L., C.W.B., and C.B.L.

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Conflict of interest

Ma.S. is Associate Editor of Human Reproduction Open; A.W.vd.B.-D received support for attending meetings and/or travel from the Dutch Cancer Society; C.B.L. is Editor-in-Chief of Human Reproduction; A.E.P.C. is Associate Editor of Human Reproduction Update, received royalties from Uptodate Hyperthecosis, and participated at the Data Safety Monitoring Board of the DSMB POEM Study; F.B. has received research support from Merck, honoraria or consultation fees from Merck Healthcare KGaA, Bensis Healthcare, CooperSurgical, and participated in an advisory board for Merck and Ferring; J.L. has received research support from Ferring, Merck, and Roche Diagnostics, consulting fees and honoraria from Ferring, participated on a Data Safety Monitoring Board or Advisory Board of the LOCI trial, is President of the AE-PCOS society, and Member of the ASRM Integrity Committee; J.M.J.S. has received honoraria from Ferring and Merck, support for attending meetings and/or travel from Ferring, Merck, and Good Life, and participated in the advisory board of Merck; L.L.v.L. received support for attending meetings and/or travel from Olympus Medical Expert training; M.M.v.R. received support for attending meetings and/or travel from Ferring; M.G. declares departmental research and educational grants from Ferring (location VUmc), unrelated to the presented work. The other authors declare no competing interests.

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