

Original Contribution

Mortality in Women Treated With Assisted Reproductive Technology—Addressing the Healthy Patient Effect

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In previous studies, investigators have reported reduced mortality among women undergoing assisted reproductive technology (ART) treatment, possibly related to selection of healthy women into ART treatment. Our aim in this study was to explore the impact of relevant selection factors on the association between ART treatment and mortality and to explore effect modification by parity. Women treated with ART in fertility clinics in Denmark during 1994–2009 ($n = 42,897$) were age-matched with untreated women from the background population ($n = 204,514$) and followed until December 31, 2010. With adjustment for relevant confounders, the risk of death was lower among ART-treated women during the first 2 years after ART treatment (hazard ratio (HR) = 0.68, 95% confidence interval (CI): 0.63, 0.74), but there was no apparent difference after 10 years (HR = 0.92, 95% CI: 0.79, 1.07). Having children prior to ART treatment was associated with markedly reduced mortality (HR = 0.45, 95% CI: 0.38, 0.53), possibly due to better health among fertile women. While the frequencies of previous medical and psychiatric diagnoses among ART-treated and untreated women were similar, differences in disease severity could explain the reduced mortality among ART-treated women, as poor prognosis would make initiation of ART treatment unlikely. The survival advantage among ART-treated women is likely a selection phenomenon rather than a biological phenomenon.

assisted reproductive technology; bias (epidemiology); comorbidity; infertility; in vitro fertilization; mortality; reproduction

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; HR, hazard ratio; IVF, in vitro fertilization.

Assisted reproductive technology (ART) treatments are widely accepted and used in Northern European countries, and the number of treatment cycles is among the highest in the world (1). Since the birth of the first live infant conceived through in vitro fertilization (IVF) in 1978, the use of ART has greatly increased; more than 450,000 IVF and intracytoplasmic sperm injection treatments were administered to European women in 2012 (2). In previous epidemiologic studies, investigators have reported that ART treatment is associated with reduced female mortality (3, 4). Because reasonably good health is a prerequisite for initiating ART treatment, the association may reflect the fact that women in good health are more likely to initiate ART treatment, which is known as the “healthy patient effect” (3, 4). Alternatively, the association may mirror a beneficial biological effect of ART treatment on female survival per se.

To date, studies on the association between ART treatment and risk of early death have been scarce and inconclusive. However, in 2 large cohort studies of IVF-treated women from the Netherlands and Australia, respectively, investigators reported lower mortality rates among women treated with ART compared with the background population (standardized mortality ratio = 0.4 (no confidence interval reported) (3) vs. standardized mortality ratio = 0.58 (95% confidence interval (CI): 0.48, 0.69) (4)). Neither of those studies adjusted for sociodemographic or health-related confounders, and heterogeneity within the group of ART-treated women was not considered. Thus, so far, the cause of the negative association between ART treatment and early death has not been determined, beyond the hypothesized “healthy patient effect.”

Our aim in the present study was to perform 2 sets of analyses to explore whether the observed reduced mortality is attributable

to better somatic and psychiatric health among ART-treated women. In the first set of analysis, we assessed the association of ART treatment with all-cause mortality according to time since ART treatment. In the second analysis, we evaluated the association between ART treatment and mortality from external causes to further investigate whether risk of death among treated and untreated women was most likely related to biological mechanisms or selection mechanisms.

METHODS

Setting

Between 1994 and 2007, only married or cohabiting heterosexual couples could be legally treated with ART by a physician in Denmark (5). From 2007 onwards, single women and lesbian couples could receive ART treatment (6). If the woman is younger than 40 years of age, up to 3 “fresh cycle” ART treatments (IVF or intracytoplasmic sperm injection) for a couple’s or a woman’s first child are financed by the Danish health-care system, as well as frozen embryo transfer treatments with any “extra” viable embryos. Hence, ART treatment is accessible to all Danish citizens regardless of income, although costs for the medication are only partly reimbursed. Self-financed treatment is available until 45 years of age for those wishing to have a second child or for females over age 40 years.

Study population

We identified all women with a date of first ART treatment in Denmark during 1994–2009 ($n = 42,904$) in the Danish National ART-Couple cohort (7). ART treatments included IVF and intracytoplasmic sperm injection, which are treatments that include ovarian hormone stimulation.

Every time a woman initiated ART treatment, 5 age-matched women with no history of ART treatment were sampled from the background population. Selection of unexposed women was random among women age-matched by year. Exposed women were followed from the date of first ART treatment onward, and unexposed women were followed from the date of treatment of their matched case. Unexposed women who subsequently went on to have ART treatment were censored from the unexposed comparison group and crossed over to contribute person-time in the exposed group ($n = 5,451$), and 5 new unexposed comparison women were sampled from the background population. The women were followed until the first occurrence of the following: death, migration, or the end of follow-up on December 31, 2010. The mean duration of follow-up was 8.8 years.

Information on treatment dates for women exposed to ART was obtained from the Danish In Vitro Fertilisation Register (8, 9). Health, migration, sociodemographic, and birth data were obtained from Danish national registers and linked to the exposure data using the unique personal identification number assigned to all residents of Denmark and recorded in all Danish registers. Information on deaths occurring during follow-up, including the date of death and the main cause of death, was obtained from the Danish Register of Causes of Death (10), which categorizes deaths according to the *International Classification of Diseases, Tenth Revision*. Two outcomes

were considered: death from all causes and death from external causes (*International Classification of Diseases, Tenth Revision*, codes W, V, Y, and X). Deaths caused by external factors are mainly accidents (for instance, traffic accidents or poisoning from unintended exposure to lethal substances).

Migration, sociodemographic, birth, and health data were obtained from the Danish Civil Registration System (11), the Medical Birth Register (12), and the Danish National Patient Register (13). Data obtained included the date of migration, partnership status (married, cohabiting, or single), educational level (low, medium, high, or highest), labor market attachment (working, unemployed, retired/unable to work, or student), number of births (continuous variable), and somatic and psychiatric hospital contacts (number of contacts for cancer, endocrine conditions, cardiovascular conditions, psychiatric conditions, neurological conditions, gastrointestinal conditions, eye/ear/skin conditions, or other diseases 2–7 years prior to study inclusion).

Potential confounders were identified prior to analyses, based on directed acyclic graphs (see Web Figure 1, available at <https://academic.oup.com/aje/article/187/9/1889/5020177>). Information on all covariates was captured prior to ART treatment.

Statistical methods

Characteristics of ART-treated and untreated women were investigated using the χ^2 test for categorical variables and the t test for continuous variables. Hazard ratios and 2-sided 95% confidence intervals were estimated using a Cox proportional hazards model. Since we used age as the underlying time scale, the crude model was already age-adjusted. The following baseline covariates were considered as confounders in the adjusted models: treatment year, educational level, labor market attachment, partnership status, parity, and comorbidity.

First, a crude analysis was conducted without confounder adjustment. Second, analyses adjusted for partnership status, treatment year, and educational level; and finally, parity and comorbidity were added to the models. We chose not to adjust for childbirth during follow-up, because it is a mediator rather than a confounder. To obtain hazard ratio estimates for death from all causes at different time points after study inclusion, we created time axes for time since first treatment and attained age using the “%stratify” macro in SAS (SAS Institute, Inc., Cary, North Carolina), which accumulates person-time stratified according to selected time-varying covariates (14). We chose to test the 2-way interaction between parity and ART treatment, because couples or women who already have children prior to treatment are more likely to be in self-financed treatment, implying increased financial barriers for treatment initiation. We tested this 2-way interaction by introducing an interaction term into the model.

Finally, we conducted an analysis using death from external causes as the outcome. If the risk of death from external causes were similar to the risk of death from nonexternal causes, this would indicate that the risk is influenced by something other than biological factors. We modeled this analysis by incorporating competing risk due to other causes of death through censoring of women who died from other causes, under the assumption that censoring is independent (15). Results of the analyses were adjusted for treatment year, educational level, labor market attachment, partnership status, and parity.

All statistical analyses were performed with SAS, version 9.4 (16).

Ethical approval

This project was approved by the Danish Data Protection Agency, the Danish National Board of Health, the Danish Medical Agency, and Statistics Denmark. The project followed the requirements of the Helsinki II Declaration (2013). According to Danish legislation, solely register-based studies do not require approval from a scientific ethical committee, because these studies do not involve direct contact with people.

RESULTS

Women in ART treatment differed from the age-matched untreated women with regard to several measures at study entry (Table 1). In particular, in comparison with untreated women, women initiating ART treatment were more likely to be married or cohabiting; they generally had a higher educational level; and they were less likely to have had children before study entry. Delayed childbearing among ART-treated women compared with untreated women was clearly apparent, because 70% of the untreated women had had at least 1 child prior to study entry, as compared with only 21% of ART-treated women. By the end of follow-up, 79% of ART-treated women and 83% of untreated women had given birth to at least 1 child. In total, 2,041 women died, with 235 deaths (0.6%) taking place among ART-treated women and 1,806 (0.9%) occurring among untreated women. Considering only death from external causes, 172 women died, 11 (0.03%) among ART-treated women and 161 (0.08%) among untreated women. Slightly more ART-treated women (2.0%) than untreated women (1.6%) had migrated. Comorbidity 2–7 years prior to study inclusion was similar among ART-treated women and women not treated with ART in all hospital contact categories, except for contacts due to urinary or reproductive problems, in which ART-treated women were more likely to be diagnosed (28% vs. 10%).

In the entire study population, crude analyses showed a lower incidence of death among ART-treated women during the first 2 years after treatment (hazard ratio (HR) = 0.65, 95% CI: 0.61, 0.70). The reduced risk persisted after adjustment for age, educational level, treatment year, partnership status, parity, and comorbidity (HR = 0.68, 95% CI: 0.63, 0.74). Adjustment for comorbidity had no impact on the results. In the adjusted model, the difference between ART-treated women and untreated women disappeared over time, and 10 years after first ART treatment the hazard ratio was no longer statistically significant (HR = 0.92, 95% CI: 0.79, 1.07) (Figure 1).

When further considering births taking place prior to study entry, we found that parous women who initiated ART treatment had the lowest risk of death during the first 2 years after their first ART treatment (HR = 0.45, 95% CI: 0.38, 0.53) as compared with untreated nulliparous women, who had the highest risk. This difference persisted until 12 years after the first ART treatment (Figure 2). During the initial 2 years following the first ART treatment, risks of death were similar among ART-treated women with no children prior to treatment and untreated women who had children, and this risk was decreased

in comparison with risk in untreated childless women (HR = 0.68 (95% CI: 0.61, 0.75) and HR = 0.67 (95% CI: 0.63, 0.72), respectively) (Figure 2). A sensitivity analysis excluding self-financed ART treatment due to female age 40–46 years did not change these results.

As a sensitivity analysis, comorbidity was included in analyses with several different period restrictions, including ≤ 5 years, ≤ 3 years, and 2–5 years prior to inclusion in the study, but this did not change the results. There was an increased frequency of diagnoses of the urinary and reproductive system among ART-treated women when the time period included the 2 years immediately before initiation of ART treatment.

The risk of death from external causes was halved among ART-treated women compared with untreated women (HR = 0.51, 95% CI: 0.40, 0.65).

A sensitivity analysis with mortality from nonexternal causes as the outcome showed results similar to those for all-cause mortality.

DISCUSSION

To our knowledge, this is the largest study to date to have examined the association between ART treatment and mortality. We found that the initially lower risk of death among ART-treated women disappeared over time and with thorough adjustment for education, partnership status, parity, and comorbidity. The risk of death from all causes was similar for ART-treated women and untreated women 10 years after treatment. Of all the women studied, those who initiated ART treatment for a second child had the lowest risk of death, which remained lower for an extended time period in comparison with women initiating ART for their first child. Women in ART treatment had a markedly reduced risk of death from external causes compared with women who did not receive ART treatment, indicating that the lower risk of death among ART-treated women is not primarily explained by biological differences.

A lower risk of death among ART-treated women has been attributed to a “healthy patient effect,” in which mostly healthier individuals seek ART treatment. A lower risk of death among ART-treated women was found in an Australian cohort study of 29,700 IVF patients followed for up to 19 years after treatment, with a standardized mortality ratio of 0.58 (95% CI: 0.48, 0.69) (4). A similar result was found in a Dutch study of deaths occurring among IVF patients as compared with the general population; the standardized mortality ratio was 0.4 (no confidence interval was reported) (3), although only deaths taking place during a 1-year follow-up period after IVF treatment were included in that study. Comparisons in these studies were made without adjustment for possible confounders such as educational level, partnership status, parity, and comorbidity; hence, the findings are comparable with the crude results from the present study.

An association between ART treatment and increased mortality has been hypothesized in several ways. Infertility may have a medical or genetic cause that also predisposes women to early death, as evidenced by previous associations with infertility and increased risks of psychiatric disorders and endometrial cancer (17). In addition, undergoing ART treatment is a strenuous process which demands personal resources (18), such as physical,

Table 1. Characteristics of Women Treated With Assisted Reproductive Technology and Age-Matched, Untreated Comparison Women, Danish National ART-Couple Cohort, Denmark, 1994–2009

Characteristic	All Women (n = 247,411)		ART-Treated Women (n = 42,897)		Untreated Women (n = 204,514)		χ^2 Test P Value
	No.	% ^a	No.	%	No.	%	
Marital status							<0.01
Married	104,847	42	20,319	47	84,528	41	
Cohabiting	65,138	26	15,188	35	49,950	24	
Living alone/single	57,459	23	3,884	9	53,575	26	
Missing data	19,967	8	3,506	8	16,461	8	
Educational level							<0.01
Highest	25,094	10	5,646	13	19,448	10	
High	43,491	18	8,968	21	34,523	17	
Medium	123,781	50	20,385	48	103,396	51	
Low	51,363	21	6,865	16	44,498	22	
Missing data	3,682	1	1,033	2	2,649	1	
Labor market attachment							<0.01
Working	197,373	80	36,474	85	160,899	79	
Unemployed	15,006	6	2,439	6	12,567	6	
Retired, unable to work	22,697	9	2,210	5	20,487	10	
Student	8,462	3	874	2	7,588	4	
Missing data	3,873	2	900	2	2,973	1	
Parity prior to study entry							<0.01
0	96,825	39	33,783	79	63,042	31	
1	51,177	21	6,818	16	44,359	22	
2	71,018	29	1,546	4	69,472	34	
3	22,500	9	538	1	21,962	11	
4	4,588	2	168	0	4,420	2	
≥5	1,303	1	44	0	1,259	1	
Age at study entry, years ^b	33.0 (18.3–46.0)		33.0 (18.5–46.0)		33.0 (18.3–46.0)		<0.01
Comorbidity 2–7 years prior to initiation of ART treatment ^c							
Any comorbid condition	83,325	34	19,475	45	63,850	31	<0.01
Endocrine system	5,072	2	931	2	4,141	2	0.06
Cancer	5,766	2	1,354	3	4,412	2	<0.01
Cardiovascular system	5,485	2	809	2	4,676	2	<0.01
Psychiatric condition	2,500	1	344	1	2,156	1	<0.01
Nervous system	4,696	2	724	2	3,972	2	<0.01
Eye, ear, or skin condition	12,644	5	2,382	6	10,262	5	<0.01
Gastrointestinal system	13,977	6	2,486	6	11,491	6	0.15
Urogenital system	31,985	13	11,796	28	20,189	10	<0.01
Other (muscles, bones, blood, respiratory system)	28,747	12	5,161	12	23,586	12	<0.01
No. of hospital contacts 2–7 years prior to study entry							<0.01
0	163,989	66	23,412	55	140,577	69	
1–5	76,575	31	17,835	42	58,740	29	
≥6	6,847	3	1,650	4	5,197	3	

Abbreviation: ART, assisted reproductive technology.

^a Column percentages are rounded and may not sum to 100.^b Values are expressed as mean (range).^c Categories are not mutually exclusive; participants could belong to more than 1 group.

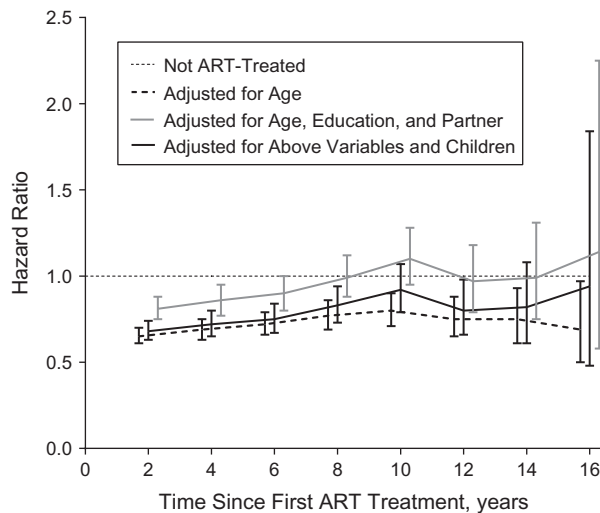


Figure 1. Risk of death from all causes during the first 16 years after initiation of assisted reproductive technology (ART) treatment, according to 3 different adjustment schemes, Danish National ART-Couple cohort, Denmark, 1994–2010. Women not treated with ART were used as the reference group (hazard ratio = 1). Bars, 95% confidence intervals.

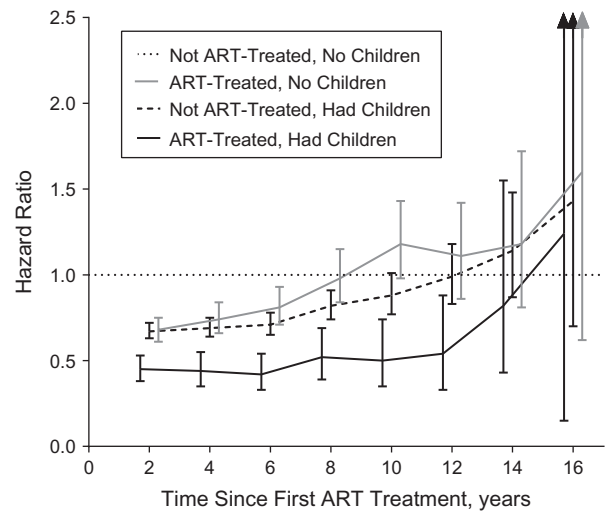


Figure 2. Risk of death from all causes during the first 16 years after initiation of assisted reproductive technology (ART) treatment, according to ART treatment status and parity at baseline, Danish National ART-Couple cohort, Denmark, 1994–2010. Hazard ratios were adjusted for educational level and partner status. Women not treated with ART were used as the reference group (hazard ratio = 1). Bars, 95% confidence intervals.

psychological, social, and relationship resources (19, 20), and there is a risk of possible adverse effects of treatment. When studying health outcomes among ART-treated women, hormonal stimulation of the ovaries is the main exposure of concern, given the fact that these hormones could influence tissues and organs other than those intended. Further, the well-documented psychological strain of undergoing ART treatment (21, 22) could increase vulnerability to psychiatric outcomes and death. The lower risk of death among ART-treated women found in the present study contradicts these hypotheses, and since a beneficial effect of ART treatment on health is unlikely, the issue of selection of women into ART treatment is a likely explanation.

In Denmark, more than half of the women initiating ART treatment have received other types of medical reproductive assistance (e.g., intrauterine insemination) prior to ART treatment (18). These women were aware of their infertility before initiating ART treatment. Therefore, they may have stopped smoking, changed their diet, lost weight, and adjusted other health behaviors to maximize the chance of conception. A similar scenario causing bias in observational studies has been described as the “healthy user” or “healthy adherer” effect, in which persons engaging in preventive interventions are more likely to engage in other healthy behaviors or to adhere to other treatments administered (23). Pregnancy planning, pregnancy, and parenthood are themselves associated with reduced mortality risk (24), which can possibly be explained both by women being generally healthy at the time and by adaptation to different health behaviors during these phases of life (25, 26). The fact that health behavior differences play an important role is underlined by our finding of a markedly reduced risk of death from external causes, which is not likely to be due to any beneficial biological mechanisms.

ART-treated women did not differ from the age-matched background population with regard to diagnoses of comorbid conditions. Medical attention due to infertility in the years leading up to initiation of ART treatment could increase the probability of detecting medical conditions with only minor symptoms in comparison with untreated women. Thus, comorbidity measured as frequency of diagnoses may be insufficient to explain the “healthy patient effect,” because it does not indicate the severity of disease and the prognosis. Diagnosis with a life-threatening disease could either prevent a woman from initiating ART treatment or diminish her wish to conceive given a short expected survival time. Additionally, initiation of ART treatment may indicate possession of the mental and physical resources needed to undergo treatment.

Previous studies have shown that physical, psychological, and social resources play a role in treatment initiation (21), as well as in treatment discontinuation (19, 27, 28). In a US study among 416 women recruited at an initial visit to a fertility clinic, screening positive for depression was found to be associated with a lower probability of initiating treatment for infertility, indicating that mental health at a subclinical level can influence treatment-seeking behavior (29). While women seeking ART treatment may not be disease-free to a greater degree than women in the background population, an increased effort and focus on improving health and avoidance of high-risk behavior in women seeking ART treatment would contribute to a decreased risk of death. Experiencing infertility is a challenge for both individuals and couples, and barriers to initiating ART treatment could be financial, social, and medical (including psychiatric) or a combination of these factors (21).

Higher socioeconomic status probably improves the likelihood of overcoming these barriers. Even with reimbursement of treatment costs, medications are only partly reimbursed, and

time spent in treatment can further influence the possibility of going to work. Women who had children prior to initiating ART treatment had the lowest risk of death, which could be explained by the selection of resourceful couples and women into self-financed ART treatment, as reimbursement of treatment costs in the Danish health-care system is made only for a couple's or a single woman's first child (6). However, sensitivity analyses excluding women aged 40–46 years at treatment initiation (not publicly financed treatment) did not change the results. Another explanation for the low mortality risk among parous women undergoing ART treatment could be that the proven fertility in these women is associated with a lower risk of death.

We chose to study time since initiation of ART treatment rather than including the number of ART treatments that a woman received as has been done by others (30–32). We argue that an increasing number of ART treatments implies a continuous selection into treatment, reflecting resilience to the strain of undergoing treatment and treatment side effects, and possibly reflecting better health. We could have analyzed data using a statistical model including time-dependent confounding. However, to avoid conditioning on, for example, future children or a future partnership, we chose to adjust the results of the analyses for baseline confounders only.

This study had several strengths, including the large sample size and the possibility of long-term follow-up using reliable national health registers, allowing for adjustment for previously diagnosed comorbidity. During 1994–2009, all ART treatments performed in Danish public and private fertility clinics were registered. This resulted in virtually full registration of Danish ART patients up to the year 2010, because IVF was only performed in very small numbers at Danish fertility clinics before 1994. In addition, because approximately 50% of all ART treatments in Denmark are offered through the public health-care system, our study was able to include women from lower socioeconomic backgrounds, enabling the assessment of relevant sociodemographic confounders.

The study also had limitations that warrant mention. As with most register-based studies, we lacked information regarding important lifestyle factors, including smoking and body mass index. However, by adjusting for socioeconomic status, we partly accounted for this problem. The comorbidity measured in this study was based on in- and outpatient hospital diagnoses. Thus, information about common diseases—such as minor psychiatric conditions, high blood pressure, or asthma treated in a general practice or by a specialist physician outside of a hospital setting—was not included. Although disease that increases the risk of early death is likely to be severe and registered in data on hospital contacts, for some patients this might not be the case.

The present study added to existing findings by demonstrating that previous crude findings on reduced mortality among women undergoing ART treatment are less pronounced after adjustment for confounders, that the survival advantage among untreated women disappears over time, and that ART-treated women have a markedly reduced risk of death from external causes, which is very unlikely to be caused by biological differences. These results suggest that the survival advantage among ART-treated women is due to selection rather than a biological phenomenon.

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