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Women With a History of Primary Infertility and Increased Rates of Bilateral Oophorectomy

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Abstract

Objective: To evaluate the association of primary infertility with subsequent bilateral oophorectomy and hysterectomy, using a population-based cohort of women with primary infertility and age-matched referent women.

Methods: The Rochester Epidemiology Project record-linkage system was used to assemble a population-based cohort of women with primary infertility diagnosed between 1980-1999 (index date). Women were age-matched (±1 y) 1:1 to a referent woman without a history of infertility or hysterectomy at the index date. Cox proportional hazards models were fit to compare long-term risks of bilateral oophorectomy and hysterectomy, respectively, between infertility cases and referents.

Results: Among both groups of 1,001 women, the mean age at index date was 29.2 ± 4.4 years. Median duration of follow-up was 23.7 years for both groups. Women with primary infertility were 1.7 times (adjusted hazard ratio (aHR) 1.69, 95% CI 1.22-2.33) more likely to have a bilateral oophorectomy compared to referent women. In a sensitivity analysis excluding women with a diagnosis of infertility related to endometriosis and their matched referents, this association persisted (aHR 1.50, 95% CI 1.06-2.14). Women with primary infertility did not have a significant increased risk of hysterectomy (aHR 0.98, 95% CI 0.79-1.23). However, risk of hysterectomy was increased in those with primary infertility related to endometriosis (aHR 1.94, 95% CI 1.12-3.34). We observed that women with primary infertility were more likely to have a hysterectomy with bilateral oophorectomy. Referent women were more likely to have a hysterectomy with ovarian conservation. Few women in either group had an isolated bilateral oophorectomy.

Conclusion: Primary infertility, with and without a diagnosis of endometriosis, is associated with an increased risk of bilateral oophorectomy. In women with endometriosis-related infertility, there is an association with future hysterectomy. These findings represent important confounders in the evaluation of long-term health outcomes related to primary infertility.

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Precis:

Women with a history of primary infertility have an increased risk of bilateral oophorectomy, and women with endometriosis-associated infertility have an increased risk of hysterectomy.

Introduction:

There is growing interest in the impact of infertility on long-term health.[1] Prior studies have shown an association between infertility and risk of mental health disorders, diabetes, renal disease, cerebrovascular disease and cardiovascular disease.[2-4] However, these studies are often limited by length of follow-up and the ability to include patient specific data including baseline health characteristics and the type and length of infertility and associated treatments. Importantly, a full understanding of long-term health outcomes associated with infertility requires adequate identification of confounding variables.

Given the frequency of hysterectomy with or without oophorectomy and known long-term health risks of these procedures, we sought to evaluate the association of primary infertility with the subsequent occurrence of these common surgical procedures. In the general population, women undergoing hysterectomy and oophorectomy have increased risks of cardiovascular disease[5], osteoporosis, psychiatric illness[6], and all-cause mortality.[7, 8] The association between primary infertility and future gynecologic surgery has not been previously investigated, and if present, may identify a compounded risk profile for women with primary infertility and their long-term health.

In this study, we utilized the Mayo Clinic Primary Infertility (MPIC) cohort, a population-based sample of women with primary infertility, and age-matched referents to evaluate the association between primary infertility and subsequent risk of gynecologic surgery, specifically hysterectomy and oophorectomy.[9] This association, if present, was hypothesized to differ by underlying infertility diagnosis and whether a woman was ever pregnant.

Methods:

The Rochester Epidemiology Project (REP) medical records-linkage system was used to create the population-based MPIC cohort of women with primary infertility.[10, 11] The establishment of the REP and its reliability have been previously published with enumerated validity when compared to other sources.[12] This study was deemed IRB exempt as it included secondary use of information (chart review). A detailed description of the cohort utilized in this study has been previously published[9] and is summarized here. A total of 3,489 women aged 18-50 with at least one diagnosis code of infertility were identified in the REP. By manual chart review, a cohort of 1,001 women had a confirmed diagnosis of primary infertility. Primary infertility was defined as an inability to conceive after 12 months of attempted conception in women aged <35 and after 6 months of attempted conception in women ≥ age 35, that was first diagnosed between January 1, 1980 and December 31, 1999 while the woman was a resident of Olmsted County, Minnesota. Secondary infertility was not included to reduce potential confounding variables, such as effects of prior treatment and prior parity on long-term outcomes. The date at their first evaluation for infertility was termed the "index date" and each woman was 1:1 age-matched (±1 y) to a randomly selected woman ("referent") residing in Olmsted County without a history of infertility or hysterectomy at index date. The matching process was made possible by the availability of a complete enumeration of the Olmsted County population using the REP Personal Timelines (i.e., the REP Census).[12] For each case with primary infertility, all age-matched (±1 y) women residing in Olmsted County on the index date were electronically identified. From that pool of potential referents, one age-matched woman was randomly selected based on a random number generator. Referent women were reviewed and replaced if they had a history of infertility at the time of index date. Referent women may have been parous or nulliparous at the time of matching.

Baseline demographic data, as of the index date, was manually collected and included age, length of attempted conception prior to evaluation, level of education, body mass index (BMI), and gynecologic surgeries prior to index date. The medical records of both groups were manually reviewed between September 2019 and November 2020. Three individuals (AA, ES and LKR) completed all chart reviews. To ensure consistency and refine the data collection tool, AA reviewed the first 50 charts in duplicate with ES and LKR. Any charts with unclear data were subsequently reviewed by AA. All data was entered into a secure electronic database. Outliers were re-reviewed by AA after the full dataset was reviewed.

The primary outcomes were subsequent hysterectomy and bilateral oophorectomy. For women undergoing hysterectomy, the date, preoperative indication, pathologic diagnosis, and uterine weight were recorded. Among women with oophorectomies, we identified the date at which both ovaries had been removed, meaning upon completion of either two separate unilateral procedures or a single bilateral procedure, which we have collectively termed bilateral oophorectomy. Complete removal of both ovaries, rather than a single unilateral oophorectomy, was deemed most important to potential long-term health risks in a premenopausal woman. The date of the last clinical visit to a REP-affiliated health care professional at the time of the chart review was also abstracted.

Patient characteristics at the time of the index date were compared between the two groups using the chi-square test or Fisher's exact test. For the analysis of each primary outcome (i.e. subsequent hysterectomy and bilateral oophorectomy, respectively), duration of follow-up was calculated from the index date to the date of procedure of interest, or the last clinical visit to a REP-affiliated health care professional for those without the procedure of interest. Cumulative incidence curves for each primary outcome, were estimated using the Kaplan-Meier method using age as the time scale. In addition, the cumulative incidence was estimated for each of the three competing outcomes (or risks) based on the first subsequent procedure per woman using a nonparametric method: i) concurrent hysterectomy and bilateral oophorectomy, ii) hysterectomy with ovarian conservation, and iii) isolated bilateral oophorectomy.[13] Cox proportional hazards models were fit to estimate the hazard ratio (HR) and 95% confidence interval for the association between primary infertility status and each primary outcome.

Multivariable Cox models were fit evaluating these associations after adjusting for the following covariates at the time of the index date, each coded as yes, no, or unknown: White race, married, 4-years of college or more, current or former tobacco use, and obesity defined as a BMI > 30 kg/m^2. Race was self-reported on patient intake forms. The Cox models were fit using age as the time scale with women entering the risk set at their respective index ages in order to more completely adjust for age. Robust sandwich covariance estimates were used in the Cox models to account for women included in both cohorts. Analyses were performed for all women combined and stratified by type of primary infertility. A sensitivity analysis was performed excluding the matched sets involving women with primary infertility related to endometriosis to evaluate whether endometriosis alone explained the associations described above.

Lastly, ever being pregnant was evaluated as a time-dependent covariate in Cox models (using time since birth) to evaluate its association with the risk of each primary outcome, respectively. Initially we included this time-dependent covariate along with primary infertility status and their interaction in each model. In addition, this covariate was evaluated in Cox models for each primary outcome, separately for primary infertility cases and referents.

All calculated p-values were two-sided. Data was analyzed using SAS version 9.4 statistical software (SAS Institute, NC; Cary, NC) and version 1.4.1103-4 of RStudio (RStudio, MA; Boston, MA).

Results:

Among both the 1,001 women with primary infertility and the 1,001 matched referents the mean age at index date was 29.2 ± 4.4 years. Sociodemographic characteristics at the time of the index date were compared between women with primary infertility and their age-matched referents (Table 1). At the time of the index date, a higher proportion of those with primary infertility were married (96.5% [966/1001] vs. 65.1% [646/993], p<0.001), had at least 4-years of college (54.6% [499/914] vs. 38.9% [361/929], p<0.001), never smoked (77.4% [770/995] vs. 64.0% [632/988], p<0.001), and were less likely to be obese (11.6% [115/988] vs. 14.9% [146/979], p=0.03) compared to the referents.

Among women with primary infertility, 883 (88.2%) had a single etiology for infertility and 118 had 2 or more. The indications included unexplained infertility (37.4%), ovulatory dysfunction (31.6%), male factor (24.6%), endometriosis (10.4%), tubal factor (6.2%), and uterine factor (2.9%). Endometriosis was diagnosed surgically. Uterine factor included known uterine fibroids, prior myomectomy, or congenital uterine anomalies. Women with primary infertility were more likely to have had a prior endometriosis surgery than referent women (3.3% vs. 0.8%, p<0.001). However, referent women were more likely to have had gynecologic surgery prior to the index date overall, specifically prior salpingectomy or dilation and curettage (D&C), either for miscarriage or abnormal bleeding (Table 1).

The median duration of follow-up after the index date was 23.7 years (interquartile range (IQR), 9.1-31.4) and 23.7 years (IQR, 9.3-30.8) for the primary infertility cases and referents, respectively. Seventeen referents were diagnosed with primary infertility after the index date for which they were selected as matched referents: 5 were diagnosed during

1985-1995 while a resident of Olmsted County and therefore also included as cases in this study, 4 were diagnosed between 1992-1998 but were not Olmsted County residents at the time of diagnosis, and 8 were diagnosed after 2000 which was outside the time period of this study. The follow-up of these 17 women in the referent group was censored at their subsequent primary infertility diagnosis date as they were no longer at risk for the outcomes as a referent woman.

The cumulative incidence of having a bilateral oophorectomy is depicted in Figure 1a. Women with primary infertility were 1.8 times (HR 1.81, 95% CI 1.36-2.42; p<0.001) more likely to have bilateral oophorectomy compared to referent women. This association persisted (adjusted HR 1.69, 95% CI 1.22-2.33; p=0.001) after adjustment for the following covariates at index date: race, marital status, education, smoking history, and obesity (Table 2). Among women who had either ovulatory dysfunction or endometriosis as the indication for primary infertility, the risk of bilateral oophorectomy was significantly increased compared to referent women, with the highest hazard ratio observed for endometriosis (Table 2). Additionally, excluding women with a diagnosis of infertility related to endometriosis and their matched referents as a sensitivity analysis confirmed the positive association between primary infertility and bilateral oophorectomy (HR 1.64, 95% CI 1.20-2.45; p = 0.002) (Appendix 1, available online at http://links.lww.com/xxx) and this persisted in the adjusted analysis (adjusted HR 1.50, 95% CI 1.06-2.14; p = 0.024). Among all women in the cohort with a bilateral oophorectomy, 7.0% had two sequential oophorectomies, including 11 of 126 (8.7%) in the primary infertility group and 3 of 73 (4.1%) in the referent group. The mean ± SD age when both ovaries were completely removed was 45.4±7.9 and 47.1±7.3 years, respectively, for the women with primary infertility compared to referent women.

Figure 1b depicts the cumulative incidence of subsequent hysterectomy. Women with primary infertility did not have a significantly increased risk of hysterectomy compared to referent women (adjusted HR 0.98, 95% CI 0.79-1.23, p=0.88; Table 2). The age at the time of hysterectomy was similar with mean±SD age of 43.2±6.9 and 43.9±7.1 years, respectively, for the women with primary infertility compared to referent women. Although the two most common primary indications for hysterectomy were the same in both groups, abnormal pre-menopausal bleeding was more common in referent women and uterine fibroids were more common in women with primary infertility. Importantly, a higher proportion of those with primary infertility underwent a hysterectomy due to endometriosis compared to the referent women (13.2% [25/190] vs. 4.5% [8/179]; p=0.003; Figure 2). The indications of tubal or uterine factor were not evaluated due to the small numbers.

When excluding the matched sets involving women with endometriosis-associated infertility for the sensitivity analysis, there was no statistically significant difference in the risk of subsequent hysterectomy (adjusted HR 0.87, 95% CI 0.68-1.10, p=0.24) between women with primary infertility and referent women (Appendix 1, http://links.lww.com/xxx). The median uterine weights were similar, 130 (IQR, 95-220) grams in women with primary infertility compared to 145 (IQR, 110-205) grams in the referent group.

The two primary outcomes of interest were further categorized into three event types based on the first subsequent procedure per woman: i) concurrent hysterectomy and bilateral oophorectomy, ii) hysterectomy with ovarian conservation, and iii) isolated bilateral oophorectomy. As shown in Figure 1c, we observed that the cumulative incidence of subsequent concurrent hysterectomy with bilateral oophorectomy was significantly higher in primary infertility cases compared to referent women (HR 1.73, 95% CI 1.27-2.37; p<0.001; adjusted HR 1.51, 95% CI 1.07-2.14; p=0.019). This association was attenuated and no longer significant in the sensitivity analysis (adjusted HR 1.25, 95% CI 0.86-1.81; p=0.25). In contrast, the cumulative incidence of subsequent hysterectomy with ovarian conservation was significantly lower in primary infertility cases compared to referent women (HR 0.73, 95% CI 0.55-0.96, p=0.026; adjusted HR 0.68, 95% CI 0.50-0.92; p=0.011) and this association persisted in the sensitivity analysis (adjusted HR 0.66, 0.49-0.90; p=0.009). Only a few women in both groups had the third event type, an isolated bilateral oophorectomy.

Hysterectomy with ovarian conservation has become more prevalent over time among the primary infertility cases. Among the 455 primary infertility cases diagnosed in 1980-1989, 105 have had a subsequent procedure including 59 (56.2%) with a concurrent hysterectomy with bilateral oophorectomy, 40 (38.1%) with hysterectomy and ovarian conservation, and 6 (5.7%) with an isolated bilateral oophorectomy. Comparatively, among the 546 primary infertility cases diagnosed in 1990-1999, 95 have had a subsequent procedure including 46 (48.4%) with a concurrent hysterectomy with bilateral oophorectomy, 44 (46.3%) with hysterectomy and ovarian conservation, and 5 (5.3%) with an isolated bilateral oophorectomy (Appendix 2, available online at http://links.lww.com/xxx).

Of the 1,001 women with primary infertility, 704 were noted to have at least one pregnancy during the available follow-up, of which 698 had a documented year reported for first pregnancy. In women with primary infertility who were ever pregnant, 42.2% (422/1,001) conceived their first pregnancy with use of fertility medications and 28.2% (282/1,001) conceived spontaneously. Of the 1,001 referent women, 794 were noted to have at least one pregnancy, of which 762 had a documented year reported for first pregnancy.

Ever being pregnant was evaluated as a time-dependent covariate in a Cox model for an association with the risk of hysterectomy and bilateral oophorectomy, respectively. For both outcomes there was evidence of an interaction effect between ever being pregnant and primary infertility status, although not statistically significant (p=0.06 for hysterectomy, p=0.08 for bilateral oophorectomy), in that the magnitude of the association between ever being pregnant and the subsequent occurrence of each outcome was different for women with primary infertility compared to the referents. Among women with a history of primary infertility, ever being pregnant was significantly associated with a decreased risk of oophorectomy (HR 0.69, 95% CI, 0.47-1.00; p=0.05) but not hysterectomy (HR 0.9, 95% CI, 0.66-1.25; p=0.54). Whereas among the referent women, ever being pregnant was not significantly associated with an increased risk of hysterectomy (HR 1.60, 95% CI 0.97-2.64; p=0.07) or oophorectomy (HR 1.42, 95% CI 0.65-3.10; p=0.38).

Discussion:

In this study, we identified an increased risk of bilateral oophorectomy for women with primary infertility compared to referent women. This association persisted when excluding women with primary infertility related to endometriosis. While there was no increased risk of hysterectomy observed overall, women with primary infertility related to endometriosis were more likely to undergo subsequent hysterectomy compared to referent women. Upon evaluating the primary outcomes as three competing outcomes or risks (based on the first subsequent procedure per woman: i) concurrent hysterectomy and bilateral oophorectomy, ii) hysterectomy with ovarian conservation, and iii) isolated bilateral oophorectomy), we observed that women with primary infertility were more likely to have a subsequent hysterectomy with bilateral oophorectomy compared to referent women. To our knowledge, there are limited data on the association of infertility and subsequent gynecologic surgery. The associations of oophorectomy and hysterectomy identified here, in women with a history of primary infertility, represent a meaningful mediator and possible confounder of long-term health risks in this population.

The long-term risks of oophorectomy have been well-described and as such, a general trend toward decreased rates of oophorectomy at the time of hysterectomy in younger women continues.[14] While oophorectomy has been shown to be associated with a decreased risk of death from ovarian cancer and breast cancer, in younger women, there is an increased risk of all-cause mortality across all age ranges.[15] All-cause mortality is likely influenced most by the presence of coronary artery disease and associated cardiovascular death, especially in women less than 45 years of age at oophorectomy and not treated with hormone therapy.[16] In our study, the relative risk of bilateral oophorectomy was highest in women with a history of primary infertility related to endometriosis or ovulatory dysfunction. However, even in the sensitivity analysis excluding women with a diagnosis of primary infertility related to endometriosis and their matched referents, this association persisted indicating an underlying diagnosis of primary infertility has an association with increased risk of bilateral oophorectomy. Importantly, age at bilateral oophorectomy was lower for women with primary infertility compared to referent women, which has shown to increase long-term health risks.[17-19]

The risk of subsequent hysterectomy did not differ between women with primary infertility and referent women, except when evaluating women with primary infertility related to endometriosis. This finding highlights a unique population with known long-term health risks ranging from increased rates of gynecologic surgery to gynecologic cancer.[20] This relationship is important as there is increasing recognition of the long-term health effects of hysterectomy, with or without ovarian conservation. Women with a history of hysterectomy and bilateral oophorectomy have a 1.12 to 1.29 hazard ratio for all-cause mortality compared to women with ovarian conservation or without prior surgery, respectively.[7, 21] Similarly, hysterectomy with ovarian conservation has been associated with increased rates of de novo hyperlipidemia, hypertension, obesity and osteoporosis.[5, 22] Lastly, hysterectomy with ovarian conservation at a young age (<40 years) has been associated with high rates of poor psychologic health, including increased rates of de novo depression and anxiety.[6, 23]

The increased risk of subsequent gynecologic surgery in women with a history of primary infertility may have multiple explanations. First and most contributory is the underlying pathology associated with infertility that is also associated with increased rates of hysterectomy and oophorectomy.[20, 24, 25] Primary infertility related to endometriosis is one obvious example. However, it is notable that the association of bilateral oophorectomy persisted even in the sensitivity analysis excluding the matched sets involving women with primary infertility related to endometriosis.

Less well-studied, the psychologic impact of primary infertility on personal perception of reproductive organ utility may provide an additional hypothesis for this association. This hypothesis is an extension of prior studies showing increased rates of body image distress and feelings of 'brokenness' shared by some patients with infertility.[26, 27] Additionally, a history of adverse childhood outcomes has been associated with increased rates of hysterectomy and oophorectomy, with many women reporting distress from their 'sexual or reproductive life'.[28, 29] Adverse childhood outcomes have not previously been evaluated in a population with infertility, and if increased, this may be a relevant contributor to our findings.

Finally, the association between infertility and infertility treatments on future cancer risk must be considered. The association between fertility treatments and ovarian tumors, specifically the extended use of clomiphene citrate and incidence of borderline tumors has been previously published.[30] However, the association between infertility and subsequent ovarian cancer is low, lacking differentiation between primary and secondary infertility and with low-certainty evidence.[31, 32] More convincingly, increased rates of endometrial cancer have been seen in women with infertility, largely driven by the shared pathophysiology of polycystic ovary syndrome (PCOS).[33, 34] In our study, the indications for hysterectomy for both gynecologic pre-cancerous or cancerous conditions did not differ between primary infertility cases and referent women, although numbers of these indications were small.

The incidence of hysterectomy in our study is comparable to prior reports; however, the primary indication for hysterectomy differed. The Oxford Family Planning Study found fibroids as the leading indication for hysterectomy followed by abnormal bleeding,[35] as did a more contemporary studies from Lombardo, Italy and from the US.[36, 37] Our study had a higher incidence of abnormal pre-menopausal bleeding followed by fibroids as the primary indication for hysterectomy. This may reflect our predominantly White population with a lower incidence of fibroids, although the prior studies did not report race, so our explanation cannot be formally explained. The quality of ultrasound imaging during this time period may have limited use and interpretation of pre-operative imaging. Additionally, the rate of myomectomy was not assessed after index data and myomectomy rather than hysterectomy may have been more commonly pursued in women with primary infertility than referent women. This is an opportunity for future study and a limitation of our findings.

The difference in incidence of oophorectomy and hysterectomy in this cohort may be best explained by a difference in decision making regarding oophorectomy at the time of hysterectomy. Interestingly, trends in oophorectomy and hysterectomy differed for women who were ever pregnant. Although not statistically significant, women with a history of primary infertility who were ever pregnant were less likely to undergo subsequent hysterectomy or oophorectomy. Conversely, referent women who were ever pregnant were more likely to undergo either hysterectomy or oophorectomy. The protective effect of pregnancy on growth of uterine fibroids, endometriosis, gynecologic cancer rates may partially explain this, while the psychologic perspective on reproductive organs may also contribute. This cohort represents one of the few historical infertility cohorts which allows for assessment of long-term health outcomes and risks associated with primary infertility. Our previous study highlighted that characteristics of our cohort of women with primary infertility are consistent with other studies of women with primary infertility, supporting its use as a representative sample for future study[9].

While the length of follow-up and number of women included in our cohort contribute to the strength and impact of our findings, our study is not without limitations. In our analysis stratified by the primary infertility indication, particularly for those with endometriosis as the indication, some models may be considered overfit using the rule of thumb of 10-15 events per each covariate included in the regression model. This overfit is evident by the wider 95% CIs and therefore some results should be cautiously interpreted. Our cohort includes a primarily White population which limits the generalizability of these associations and may weaken the risks of future hysterectomy, which are higher in African American women.[38] Future work in other historical cohort studies is needed to confirm our findings in a more racially diverse cohort.

In summary, the effects of oophorectomy and hysterectomy on overall health and all-cause mortality may present an important confounding variable in studies assessing long-term risks of infertility and should be included in future studies evaluating long-term health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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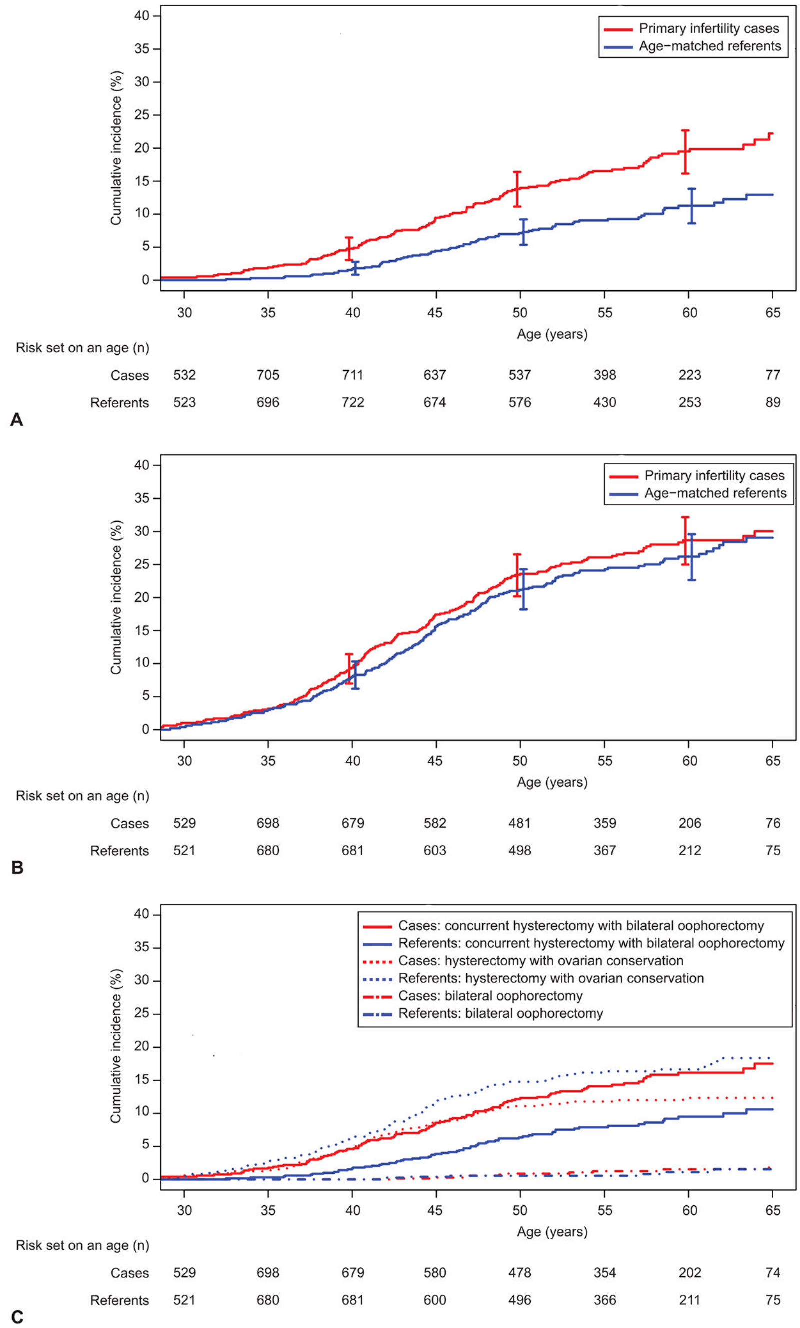

Figure 1:

Cumulative incidence of subsequent bilateral oophorectomy (**A**), hysterectomy (**B**), and the competing risks (**C**) of which procedure occurs first in women with primary infertility compared to age-matched referent women, using age as the time scale. **A.** Case vs referent: hazard ratio (HR) 1.81, 95% CI 1.36–2.42. **B.** Case vs referent: HR 1.08, 95% CI 0.88–1.32. **C.** Concurrent hysterectomy with bilateral oophorectomy; case vs referent HR 1.73, 95% CI 1.27–2.37. Hysterectomy with ovarian conservation; case vs referent HR 0.73, 95% CI 0.55–0.96.

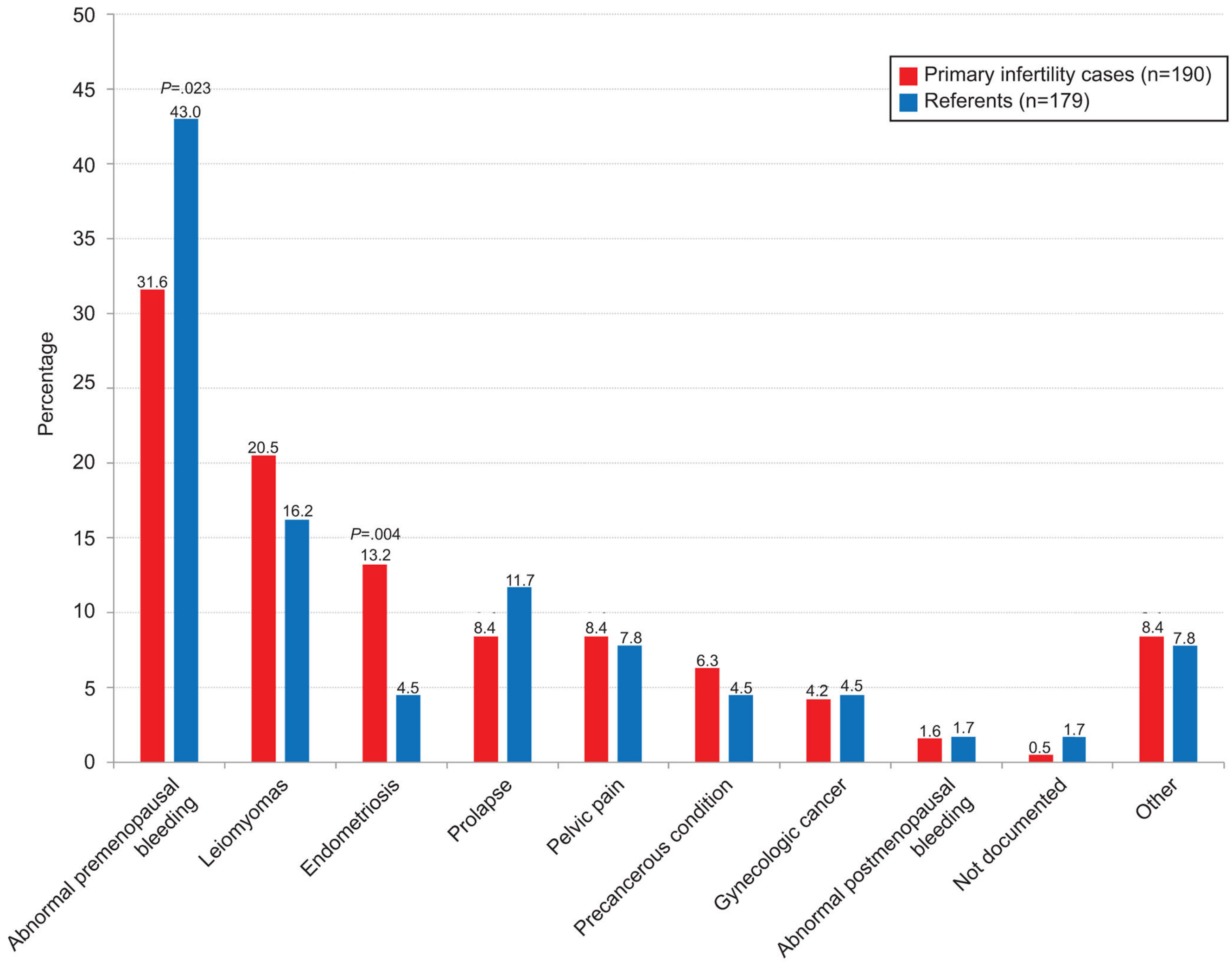

Figure 2:
Primary indication for hysterectomy.

Table 1.

Sociodemographic characteristics and gynecologic surgery history at the time of the index date of women diagnosed with primary infertility between 1980 and 1999 and age-matched female referents.

Characteristic at the index date†	Primary infertility (N=1001)	Referent (N=1001)	p value‡
Age (years)			--^
Mean ± SD	29.2 ± 4.4	29.2 ± 4.4	
Range	(18.4-45.9)	(18.2-46.1)	
Race			0.045
American Indian or Alaskan Native	1 (0.1%)	6 (0.6%)	
Asian	28 (2.8%)	23 (2.3%)	
Black	11 (1.1%)	5 (0.5%)	
Native Hawaiian or Pacific Islander	0 (0.0%)	1 (0.1%)	
Unknown or chose not to disclose	151 (15.1%)	191 (19.1%)	
White	797 (79.6%)	761 (76.0%)	
None of the Above	13 (1.3%)	14 (1.4%)	
Ethnicity			0.016
Hispanic or Latino	25 (2.5%)	9 (0.9%)	
Not Hispanic or Latino	726 (72.5%)	722 (72.1%)	
Unknown or chose not to disclose	250 (25.0%)	270 (27.0%)	
Marital Status			<0.001
Single	15 (1.5%)	337 (33.7%)	
Married	966 (96.5%)	646 (64.5%)	
Partnered (not Married)	20 (2.0%)	10 (1.0%)	
Not documented	0 (0.0%)	8 (0.8%)	
Level of education			<0.001
Less than high school	12 (1.2%)	33 (3.3%)	
High school graduate	129 (12.9%)	201 (20.1%)	
Some college	274 (27.4%)	335 (33.5%)	
College (4-yr) graduate	340 (34.0%)	226 (22.6%)	
Beyond college	159 (15.9%)	135 (13.5%)	
Not documented	87 (8.7%)	71 (7.1%)	
Tobacco use			<0.001
Current	153 (15.3%)	262 (26.2%)	
Former	72 (7.2%)	94 (9.4%)	
Never	770 (76.9%)	632 (63.1%)	
Not documented	6 (0.6%)	13 (1.3%)	
BMI (kg/m^2)			0.014
Mean ± SD	24.1 ± 5.7	24.8 ± 5.9	
Less than 18.5	49 (4.9%)	26 (2.6%)	
18.5 - 24.9	645 (64.4%)	617 (61.6%)	
25 - 29.9	179 (17.9%)	190 (19.0%)	

Characteristic at the index date†	Primary infertility (N=1001)	Referent (N=1001)	p value‡
30 - 39.9	88 (8.8%)	118 (11.8%)	
40 or more	27 (2.7%)	28 (2.8%)	
Not documented	13 (1.3%)	22 (2.2%)	
Gynecologic surgery history			
At least one of the following	91 (9.1%)	120 (12.0%)	0.035
Laparoscopic drilling	1 (0.1%)	0	>.99
Cystectomy	24 (2.4%)	15 (1.5%)	0.15
Unilateral oophorectomy	13 (1.3%)	6 (0.6%)	0.11
Salpingectomy	11 (1.1%)	44 (4.4%)	<0.001
Dilation and curettage	31 (3.1%)	58 (5.8%)	0.003
Myomectomy	7 (0.7%)	0	0.016
Endometriosis resection	33 (3.3%)	8 (0.8%)	<0.001

†The index date for each matched pair (case and referent) was defined as the date when the infertility case was first diagnosed with primary infertility.

‡Comparisons between the two groups were evaluated using the two-sample t-test for BMI and the chi-square test or Fisher's exact test for all other characteristics.

^Age was not statistically compared as each infertility case was 1:1 age-matched (±1 y) to a referent woman.

Table 2.

Comparison of the cumulative incidence of bilateral oophorectomy and hysterectomy between women with primary infertility and age-matched referent woman, overall and within type of primary infertility strata

Outcome	Primary infertility group			Referent group			Unadjusted analysis†		Adjusted analysis‡	
	No. at risk	Total person-years	No. of events	No. at risk	Total person-years	No. of events	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Overall										
Bilateral oophorectomy	1,001	19,760	126	1,001	20,458	73	1.81 (1.36 - 2.42)	<0.001	1.69 (1.22 - 2.33)	0.001
Hysterectomy	1,001	18,707	190	1,001	18,889	179	1.08 (0.88 - 1.32)	0.46	0.98 (0.79 - 1.23)	0.88
Type of infertility= Ovulatory dysfunction										
Bilateral oophorectomy	316	6300	35	316	6445	16	2.27 (1.26 - 4.08)	0.006	2.25 (1.14 - 4.41)	0.019
Hysterectomy	316	5932	58	316	6041	51	1.18 (0.81 - 1.71)	0.39	1.02 (0.68 - 1.51)	0.93
Type of infertility= Male factor										
Bilateral oophorectomy	246	4864	35	246	5048	19	1.94 (1.11 - 3.40)	0.020	1.59 (0.87 - 2.90)	0.13
Hysterectomy	246	4598	51	246	4642	44	1.19 (0.80 - 1.78)	0.39	1.08 (0.71 - 1.64)	0.71
Type of infertility= Endometriosis										
Bilateral oophorectomy	104	1828	27	104	2028	10	2.95 (1.45 - 6.01)	0.003	2.77 (1.32 - 5.81)	0.007
Hysterectomy	104	1749	33	104	1838	20	1.72 (1.00 - 2.98)	0.051	1.94 (1.12 - 3.34)	0.017
Type of infertility= Unexplained										
Bilateral oophorectomy	374	7506	36	374	7881	29	1.33 (0.82 - 2.16)	0.25	1.25 (0.70 - 2.22)	0.45
Hysterectomy	374	7082	61	374	7272	65	0.97 (0.68 - 1.37)	0.86	0.84 (0.56 - 1.26)	0.40

† Hazard ratios were estimated using Cox proportional hazards models with age as the time scale.

‡ Hazard ratios were estimated using Cox proportional hazards models with age as the time scale and adjusted for the following covariates at the time of the index date, each coded as yes, no, or unknown: White race, married, 4-years of college or more, current or former tobacco use, and obesity defined as a BMI > 30 kg/m^2