Published in final edited form as:
Am J Obstet Gynecol. 2011 November ; 205(5): 476.e1–476.e8. doi:10.1016/j.ajog.2011.06.002.

ROTATING NIGHTSHIFT WORK AND THE RISK OF ENDOMETRIOSIS IN PREMENOPAUSAL WOMEN

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Abstract

Objective—To prospectively study the association between rotating nightshift work and endometriosis risk within the Nurses' Health Study II.

Study Design—89,400 women without diagnosed endometriosis at baseline, among whom 2,062 laparoscopically-confirmed cases documented during 16 years of follow-up formed our study population.

Results—Overall, there was no association between rotating nightshift work and risk of endometriosis. When case women were categorized by infertility status, risk was elevated among women with concurrent infertility and ≥5 years of rotating nightshift work (RR=1.71; 95%CI=1.18–2.49; P_{trend}=0.005), compared to women without rotating nightshift work. In contrast, there was no association among women without reported infertility ($P_{heterogeneity}$=0.003).

Conclusions—Women who work rotating nightshifts for ≥5 years may have a modestly elevated risk of endometriosis if concurrently infertile. However, the relation between shiftwork, endometriosis, and infertility is complex, and the potential for bias due to a healthy or infertile worker effect needs to be considered.

Keywords

melatonin; night work; endometriosis

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INTRODUCTION

Endometriosis is the diversion of functioning endometrial tissue into the abdominal cavity. Up to one in ten women of childbearing age suffers from this often painful and infertility-associated condition,[1] making it the third leading cause of gynecologic hospitalization in the United States.[1] Few protective factors have been identified to date, among those later age at menarche, longer menstrual cycles, older age, higher body mass index, greater parity, and longer duration of lactation.[2]

The pathogenesis of endometriosis is multifactorial, encompassing mechanical, hormonal, immunologic, and inflammatory influences. Sampson proposed the theory of retrograde menstruation in 1927, arguing that the subsequent implantation and growth of endometriotic tissue on extra-uterine structures leads to the development of the disease.[3] While laparoscopy has shown that more than 90% of women exhibit retrograde menstruation,[4] only a small percentage go on to develop endometriosis – suggesting that other factors contribute to an individual's susceptibility to the disease.

Strong circumstantial evidence indicates that endometriosis depends on circulating steroid hormones. Endometriosis plaques have been shown to have estrogen, progesterone, and androgen receptors and have been shown to grow in the presence of estrogen but atrophy when exposed to androgens.[5–8]

In addition, there is evidence to suggest that endometriosis is dependent on immunologic and inflammatory responses,[9] although the temporal sequence is not clear. Case-control studies have observed abnormal levels and function of growth factors, macrophages, and pro-inflammatory cytokines in the peritoneal fluid and serum of women with endometriosis[5, 7, 10–12] Nightshift work decreases melatonin levels.[13] As melatonin has potential anti-estrogenic activities and inhibits aromatase activity in mammary tumors,[14] nightshift workers may experience altered aromatase activity and higher estrogen levels that would promote endometriosis growth. On the other hand, reduced levels of melatonin among nightshift workers may increase adiposity,[15–18] reducing endometriosis risk, particularly among concurrently infertile women among whom greater body size has been observed to be associated with a greater magnitude of risk reduction. In rats and mice with surgically induced endometriosis, exogenous melatonin appears to induce atrophy of the endometriotic lesions presumably via regulation of matrix metalloproteinase-9.[19]

A recent population-based case-control study reports any type of nightshift work to be associated with a 48% increased risk of endometriosis.[20] Here, we present a prospective evaluation of the relationship between night work and endometriosis risk in a large cohort of premenopausal women. Using data collected from the Nurses' Health Study II, we have attempted to clarify the relation between rotating nightshift work and laparoscopically-confirmed endometriosis.

MATERIALS AND METHODS

Study population and data collection

The Nurses' Health Study II (NHS II) is a prospective cohort study that began in 1989, when 116,608 registered female U.S. nurses of ages 25–42 and residing in one of 14 states were enrolled. The study was designed to prospectively examine the effects of oral contraceptive use and other life style factors on chronic diseases, particularly cancers and cardiovascular diseases. Since 1989, these predominantly Caucasian nurses have completed biennial mailed questionnaires that include items about their health status, medical history, and known or suspected risk factors for cancer, heart disease, and other pathologies.[21] The questions

include age, age at menarche, parity, age at first birth, weight, height, menopausal status, family history of breast cancer, and personal history of benign breast disease and cancer, among others. Every two years, follow-up questionnaires were sent to cohort members to update the information on potential risk factors, identify newly diagnosed case subjects, and record other major medical events. Further details of the cohort are described elsewhere[22]. Response rates to the NHSII questionnaires are at 90% throughout follow-up. This research was approved by the Institutional Review Board of Brigham and Women's Hospital.

Case ascertainment and analytic definition

In 1993, the women were first asked if they had "ever had physician-diagnosed endometriosis." If "yes," they were asked to report when the diagnosis had occurred (before September 1989, September 1989–May 1991, and June 1991–May 1993. which correspond to the follow-up periods) and if it had been confirmed by laparoscopy – a standard surgical method for diagnosing endometriosis.[23, 24] These questions were asked again in each subsequent questionnaire.

As previously described,[2] in March 1994 we conducted a study to validate self-reported endometriosis diagnosis within the NHSII cohort. Supplementary questionnaires were mailed to 200 women who were randomly selected from the then 1,766 cases who had reported incident diagnosis. Among those who reported laparoscopic-confirmation and for whom records were received and reviewed (n=105), a laparoscopic diagnosis of endometriosis was confirmed in 96%. However, among those women without laparoscopic confirmation (n=26), evidence of clinical diagnosis was found in only 54% of the records. Severity data (defined by the staging system outlined by the American Society for Reproductive Medicine) suggested that the majority of laparoscopically-confirmed cases (61%) had minimal or mild disease. Requests for permission to review medical records were also sent to any woman who indicated that she had had a hysterectomy during the two year interval of reported endometriosis diagnosis. A diagnosis of endometriosis at the time of surgical procedure was confirmed in 80% (n=144/181) of the records received. However, endometriosis was the primary indication for hysterectomy in only 6% (n=9/163) of women for whom indication information was available.

Based upon these validation results, self-reported physician-diagnosed endometriosis without laparoscopic confirmation may be misclassified substantially. In addition, allowing women who report endometriosis and a hysterectomy in the same follow-up period to be cases might yield spurious results, because it would be unclear if the associated risk factors are related to endometriosis or to the pathology for which the hysterectomy was performed. Therefore, to reduce the magnitude of misclassification and prevent confounding by indication for hysterectomy, analyses of incident diagnosis of endometriosis were restricted to those women who reported laparoscopic confirmation of their diagnosis.

Within this restricted case definition, the relation between endometriosis and infertility status is complex. At baseline, the prevalence of infertility (defined as attempting to become pregnant for >1 year without success) was greater among women with laparoscopic confirmation (20%) than among those who were clinically diagnosed without laparoscopic confirmation (4%). Approximately 20% of all infertile women are found to have endometriosis.[25] While pelvic pain information is not available in the NHSII cohort, cases with no infertility who have had a laparoscopic diagnosis are more likely to have experienced pelvic pain symptoms, otherwise an invasive surgical evaluation would not have been conducted. In addition, among cases with infertility we may also assume that had these women not attempted to become pregnant, a large proportion may never have received a laparoscopic diagnosis of endometriosis. Under these assumptions, we believe that endometriosis with infertility may be indicative of asymptomatic disease secondary to other

primary causes of infertility and the risk factors for endometriosis with infertility could differ from those for endometriosis without concurrent infertility. In addition, the setting of infertility evaluation introduces the potential for detection/diagnostic bias. Hence, we looked at risk factors separately by these two "subtypes" of endometriosis in a polytomous outcome fashion – 1) cases who had never reported infertility before their endometriosis diagnosis, and 2) cases with concurrent infertility. In addition, we alternatively treated infertility as a typical effect modifier, stratifying the entire study population by report of having had a clinical evaluation for infertility. Within this cohort, self-reported infertility was validated in a study of 100 randomly selected women who reported ovulatory infertility -- 95% of the self-reports were confirmed through medical record review.[26]

Assessment of nightshift working status

Detailed information on total years during which study participants had worked on rotating nightshifts was available from the 1989 questionnaire, with updates in 1991, 1993, and 1997. The 1991 questionnaire collected information about total number of months during which the nurse had worked rotating nightshifts for at least 3 nights per month, in addition to having worked days or evenings in that month (since June 1989). The prespecified categories for total numbers of months working on rotating nightshifts were "none, 1–4 months, 5–9, 10–14, 15–19, and 20 months or more." Identical questions were posed in 1993 and 1997 (since June 1989 and June 1995, respectively). Night work information was assessed retrospectively for the time-periods 1993–1995 and 1997–1999: nurses were asked on the 2001 questionnaire about the number of months they had worked on rotating nightshifts during these time periods. Specifically, nurses were asked "During the following time periods, how many months have you worked *rotating* nightshifts (at least 3 nights/month in addition to other days and evenings in that month)?" and "Did you work *permanent nightshifts* for 6 or more months during any of these time periods?"

Statistical analysis

Data for these analyses were collected in the NHSII cohort from September 1989 to June 2005. Participants who reported the diagnosis of endometriosis or a history of infertility prior to September 1989 were excluded from all analyses. We excluded women with a history of infertility because of the strong correlation between infertility and diagnosis of endometriosis via laparoscopy as well as to reduce the potential for a healthy worker effect. Alternatively, we conducted analyses that did not censor at report of infertility evaluation (at baseline or during follow-up as described below) nor polytomize the case women by mode of diagnosis (indication of surgical evaluation during an infertility work-up versus not) but rather treated infertility as a typical effect modifier – thus stratifying the entire study population into groups who had never or ever had reported having had a clinical evaluation for infertility.

Analyses were also restricted to those who were premenopausal and had intact uteri, because the occurrence of endometriosis after hysterectomy or in postmenopausal women is rare. Women with prior cancer diagnoses, other than non-melanoma skin cancer and women who did not report their rotating nightshift work history on the baseline 1989 questionnaire were also excluded. Person-months at risk were calculated from entry into the cohort until independently confirmed death or cancer diagnosis (other than non-melanoma skin cancer), or self-reported laparoscopically-confirmed endometriosis diagnosis, hysterectomy, or the onset of menopause. Women who reported physician-diagnosed endometriosis with no laparoscopic confirmation were censored at the time of that report but were allowed to re-enter the analysis population with their interim person time if they reported laparoscopic confirmation on a subsequent questionnaire. In addition, because infertility is so strongly correlated with diagnosis of endometriosis via laparoscopy, to minimize detection bias, we

censored at self-report of clinical infertility evaluation. Therefore, in our primary analysis, our comparison group consists of women with neither diagnosed endometriosis nor infertility, allowing for a more homogeneous comparison group as we have previously described in detail.[2] In a secondary analysis, we included only women who had had an infertility evaluation to equalize the possibility of secondary detection between cases and controls.

Because rotating nightshift workers are less likely to entrain their circadian rhythms than are permanent night workers, women who reported having worked more than 6 months of permanent night work were excluded. Rotating shift work information was updated by using baseline 1989 information on total number of years having worked rotating night work up to then and adding months as reported on subsequent questionnaires.

Incidence rates for each exposure category were computed as the number of incident cases divided by the person-time accumulated. Time-varying Cox proportional hazards models treating age in months and 2-year questionnaire period as the time scale were used to estimate multivariate (MV) incidence rate ratios (RR) and to calculate 95% confidence intervals (CI), after adjusting simultaneously for confounding variables. Tests for trend in ordinal categorical exposures were calculated by creating an ordinal variable in which the median value or midpoint of each category was assigned to all participants in that group. Tests for heterogeneity comparing the effect estimates among cases who never reported infertility with effect estimates among cases having concurrent infertility were calculated with a Wald statistic referred to a chi-squared distribution with 1 degree of freedom.

To evaluate if the night shiftwork and endometriosis associations varied by levels of other risk factors, stratified analyses were conducted, and likelihood ratio tests comparing the model with both the main effects and the interaction terms to that with the main effects only were calculated.

RESULTS

We documented 2,062 incident laparoscopically verified endometriosis cases during 16 years of follow-up. At baseline (1989), women who had never worked on rotating nightshifts accounted for 38% of the person-years of follow up, 28% worked 1–2 years, 20% 3–5 years, and the remaining 14% reported having worked rotating nightshifts for more than 5 years. Women who worked rotating shifts were similar in their characteristics to those who had never done such work (Table 1). However, there were slightly fewer women who reported smoking or being nulliparous among the never nightshift workers and they tended to be leaner than women with 5 or more years of rotating nightshift work (Table 1).

Table 2 shows the relationship between cumulative updated years of rotating nightshifts and endometriosis. Overall, there was no apparent association with endometriosis risk with increasing duration of rotating nightshift work (Table 2). However, these risks differed depending on the infertility status of a woman. In multivariate analyses, among women who never reported infertility, a higher cumulative duration of nightshift work did not appear to increase a woman's risk of endometriosis (5+ years of rotating night work vs. never, RR=0.83; 95% CI=0.68–1.01; P_{trend} = 0.07), rather, suggesting a null to inverse association. By contrast, for women with concurrent infertility, we observed a 71% increased risk of endometriosis (5+ years of rotating night work vs. never, RR=1.71; 95% CI=1.18–2.49; p-value, test for linear trend=0.005; $P_{heterogeneity}$ = 0.003). When these analyses were re-analyzed without censoring at report of infertility (such that the comparison group included both women who had never reported infertility previously and those who had), the associations among never infertile women were unchanged (RR=0.83; 95% CI=0.69–1.00),

while among concurrently infertile women they were attenuated but remained statistically significant (RR=1.28; 95% CI=1.01–1.62; $P_{heterogeneity} = 0.01$).

Alternatively, Table 3 shows the relationship between cumulative updated years of rotating nightshifts and endometriosis within strata of never versus ever having reported a clinical evaluation for infertility. The risks still subjectively differed depending on whether the case and comparison women had never or ever reported a clinical evaluation of infertility. There was still the suggestion of a null or inverse relation among those who had never had an infertility work-up (5+ years of rotating night work vs. never, RR=0.86; 95% CI=0.70–1.04; $P_{trend} = 0.16$). However, among those who had ever had a clinical evaluation for infertility, the magnitude of the effect was attenuated considerably (5+ years of rotating night work vs. never, RR=1.10; 95% CI=0.89–1.36; $P_{trend} = 0.60$; $P_{heterogeneity} = 0.21$).

In stratified analyses, we observed no effect modification by parity, BMI, smoking history, recent physical exam, or oral contraceptive use (data not shown).

It is conceivable that women stopped working nightshifts due to early symptoms associated with endometriosis. If true, such ‘healthy worker effect’ would have biased our results toward the null. To address this hypothesis, we repeated our analyses after excluding the first 4 years of follow-up after the baseline report on night work (1989–1993). However, when analyzing the relation between number of nights worked as assessed in 1989 and the risk of endometriosis from 1993 through 2003, this 4-year latency period was associated with a similar increase in endometriosis risk among those with concurrent infertility and a null to protective non-significant association among those who never reported infertility (data not shown).

To explore the role of sleep in these associations, we made use of information about average sleep duration and adequacy of sleep as well as sleepiness as queried on our 2001 questionnaire. When restricting baseline to 2001, in prospective analyses (though limited by small cases numbers), the association between sleep duration and endometriosis risk appeared U-shaped: in multivariate analyses, both women who reported sleeping 5 or fewer hours on average (RR=1.61; 95% CI=0.88–2.92) as well as women with 9 or more hours of average sleep (RR=2.10; 95% CI=1.26–3.51) experienced a higher risk of endometriosis. Power was limited in these analyses to explore effect modification by fertility status, though risks appeared similar among women never reporting infertility and those with concurrent infertility (data not shown).

Neither snoring, inadequate sleep duration, nor number of hours of daily activities affected by sleepiness was associated with endometriosis risk in these analyses. When using our 2001 sleep information retrospectively, 5 or fewer average hours of sleep (RR=1.39; 95% CI=1.14–1.68) and 9+ hours sleep (RR=1.32; 95% CI=1.08–1.60) were significantly associated with endometriosis risk, though slightly weaker. With more cases in these analyses we were able to explore effect modification by fertility status; interestingly, the increases in risk with longer and shorter sleep duration appeared to be restricted to women who never reported infertility, and were not apparent in women with concurrent fertility (data not shown; $P_{heterogeneity} = 0.17$).

DISCUSSION

In this large prospective cohort study with detailed and updated information on nightshift work, the risk of laparoscopically verified endometriosis was found to be significantly elevated in women with concurrent infertility who worked for 5 or more years on rotating nightshifts, compared with those who never worked rotating nightshifts and had no infertility. However, among women who never reported infertility a null or potentially

protective association between rotating nightshifts and endometriosis risk was observed. The finding among infertile cases is consistent with previous study suggesting a link between night work and endometriosis (insert cite), however, to our knowledge, this is the first prospective report on this association in premenopausal women and the first to evaluate the relation by infertility history. The influence of infertility is complex, as we observed attenuation of the relation between rotating nightshifts and endometriosis when the data were evaluated through simple stratification by clinical evaluation of infertility rather than via polytomization of only the case women by infertility status during the period of diagnosis.

Evidence from observational studies of occupational light exposure at night and the risk of endometriosis is still scant. To date, only one population-based case-control study has reported on this relationship[20] and describes an elevated endometriosis risk associated with night work. Specifically, among 235 premenopausal women with surgically confirmed endometriosis and 545 controls, the authors found any night work to be associated with a 48% increased risk of endometriosis (OR=1.48; 95% CI=0.96–2.29). More recently, a case-control study nested in a large health-maintenance organization in the US reported an increased risk of endometriosis to be associated with having worked as a flight attendant or nurse or health aide, but no information on shift work history was available in these analyses.[27]

Our results suggest no overall association between shiftwork and endometriosis, with the possibility of a differential effect between women diagnosed with no history of infertility compared to those whose endometriosis was diagnosed at the time of incident infertility clinical evaluation. The results from our study are compatible with these previous reports. That we see a higher risk of endometriosis among rotating night workers with concurrent infertility suggests that the pathophysiology of infertility may interact with the physiologic disturbances of nightshift work that underlie endometriosis.

Higher estrogen levels have been linked to an increased endometriosis risk.[28] Rotating night work may increase estrogen levels by lowering melatonin levels.[29, 30] Experimental studies corroborate this notion, and several studies lend direct[31, 32] and indirect evidence[33, 34] in support of an inverse association between melatonin and estrogen levels. Melatonin also interferes with the local synthesis of estrogens by regulating the activity of aromatases, the enzymes controlling the conversion from androgenic precursors to estrogens, thus behaving as a selective estrogen enzyme modulator or aromatase inhibitor.[35–37] Aromatase activity also has been implicated in the pathophysiologic establishment of endometriosis.[28]

Several lines of evidence suggest a positive association between melatonin and androgens; in women with polycystic ovarian syndrome (a hyperandrogenic disorder), testosterone was the only hormonal correlate of melatonin levels among many hormones tested.[38] Thus, the lower melatonin levels observed in rotating nightshift workers are in line with the hyperestrogenic/hypoandrogenic hormonal state typically associated with endometriosis, however, our observed association was only within women who had been diagnosed with endometriosis concurrent to undergoing a clinical evaluation for infertility.

Although not statistically significant, the suggestion of an inverse relation between night shiftwork and endometriosis among women who have never reported infertility may be indicative of the influence of the healthy worker effect. Laparoscopic confirmation of endometriosis among those never experiencing infertility is restricted to those with clinical pain symptoms of endometriosis – chronic pelvic pain, severe dysmenorrhea, dyspareunia, painful urination, and/or painful defecation. It may be that women with chronic pain of a level that surgical investigation is warranted are less likely to be able to maintain rotating

nightshiftwork, therefore biasing toward observation of a “protective” association within this case sub-group.

Conversely, among infertile women, there may be an ‘infertile worker effect,’ that women with fertility sufficient to have children take themselves out of the workforce, or at the very least, out of work schedules that are variable or unpredictable such as rotating shift work. This could cause a bias toward a positive association of nightshift work with endometriosis among those with concurrent infertility. We did observe a greater prevalence of nulliparity at baseline among rotating shiftworkers. However, the majority of infertile women were parous (i.e. incidently reporting secondary and not primary infertility). Additionally, we evaluated effect modification by parity and observed no differences in the association between rotating shiftwork and endometriosis among the parous and nulliparous women, which would argue against such a bias. Given attenuation of the association when evaluated alternatively by employing simple stratification by clinical infertility work-up and the potential for detection/diagnostic bias, it is difficult to interpret the observed detrimental effect among cases with concurrent infertility.

For all endometriosis case women, whether those presenting for diagnosis solely with pain symptoms or those diagnosed concurrently with an infertility evaluation, it is impossible to identify the exact point of disease onset. Therefore, the temporality between reported nightshift work and the incidence of endometriosis is opaque. When analyses excluded the first 4 years of follow-up after the baseline report on night work, this 4-year latency period was associated with a similar increase in endometriosis risk among those with concurrent infertility and a null to protective non-significant association among those who never reported infertility. However, this may not be a long enough latency period to establish the relevant exposure window for initiation/promotion of endometriosis.

Although we did not validate self-reported duration of rotating nightshifts, it is likely that our results are accurate, because other self-reports were highly accurate in a similar cohort,[39] and previous validations of similar questions (e.g. electric blanket use)[40] have shown reasonable reproducibility. Moreover, the prospective design of our study eliminates recall bias. On the other hand, assessment of exposure status with regard to working on rotating nightshifts can only be a rough estimate, and misclassification is likely.

A potential limitation in our study is that women who work more frequently on nightshifts may differ from women who do not in ways that influence risk of endometriosis but for which we were not able to control. Alternatively, given the currently known differences in the risk profile of women with endometriosis with and without concurrent infertility,[2] it is conceivable that our findings could be explained by uncontrolled confounding. For example, even though we controlled for known potential confounding factors, uncontrolled confounding may stem from differences in socioeconomic status or other differences in lifestyle that we were not able to consider.

In conclusion, working on rotating nightshifts was associated with a modestly increased risk of endometriosis among the female nurses with concurrent infertility in our cohort. This effect was attenuated when evaluated among all women who had ever had a clinical evaluation for infertility. The findings from our study, including sub-analyses and in combination with the results of the previously published case-control study, reduce the likelihood that this association is due solely to chance but interpretation remains unclear. The possibility of bias due to a healthy worker effect or an infertile worker effect needs to be evaluated more finely in future studies. Since endometriosis constitutes a large disease burden in the U.S., and since a sizable portion of workers engage in shift work, further

studies examining the relationship between light exposure and endometriosis risk through the melatonin pathway are warranted.

Acknowledgments

We are indebted to the participants of the Nurses' Health Study II for their continuing outstanding dedication to the study.

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Table 1

Age and age-standardized* characteristics at baseline (1989) according to rotating shift work status among 89,400 premenopausal women in the Nurses' Health Study II*.

	Duration of work on rotating nightshifts (years)		
	Never	**1–4.9 years**	**≥5 years**
	N=34,404	N=43,695	N=11,301
Age, years (mean)	33.9	33.6	35.0
BMI at age 18, kg/m^2 (mean)	21.2	21.2	21.8
Adult BMI, kg/m^2 (mean)	23.8	23.8	24.9
Age at menarche <12 years (%)	23.6	23.7	25.3
Age at menarche, years (mean)	12.4	12.4	12.4
Ever used oral contraceptives (%)	82.4	82.6	81.2
Nulliparous (%)	28.1	31.5	36.6
Parity†, number of children (mean)	2.1	2.1	2.0
Age at first birth, years (mean)	25.1	25.5	25.6
Regular menstrual cycles, ages 18–22 (%)	79.1	78.0	76.5
Short cycles‡, ages 18–22 (<26 days) (%)	11.4	12.1	13.0
Alcohol, grams/day (mean)	3.0	3.3	3.1
Packyears smoked§ (mean)	10.9	10.9	11.5
Current smokers (%)	12.0	12.8	16.2
Physical activity, MET-h/wk (mean)	23.0	26.2	28.3

*Age-standardized according to four categories of age at baseline (<30, 30–34, 35–39,40+ y).

†Among parous women only.

‡Short cycles defined as <26 days.

§Among smokers only.

TABLE 2

Adjusted relative risks (RRs) and 95% confidence intervals (CIs) of endometriosis risk by rotating nightshift work in three categories among premenopausal women in the Nurses' Health Study II (1989–2003), excluding permanent night workers.

	Case definition								
	All women (no past infertility)				No past or concurrent infertility[a]		Concurrent infertility[a]		
Duration of rotating nightshift	Cases	Person years	Age-adjusted RR[b]	MV RR (95% CI)[c]	Cases	MV RR (95% CI)[c]	Cases	MV RR (95% CI)[c]	p[d]
Never	494	254,786	1.00	1.00	408	1.00	74	1.00	0.003
1–4.9 years	650	333,477	1.02 (0.90, 1.14)	1.00 (0.89, 1.13)	506	0.97 (0.85, 1.10)	125	1.22 (0.91, 1.63)	
≥5 years	186	96,861	1.05 (0.89, 1.25)	0.97 (0.82, 1.16)	130	0.83 (0.68, 1.01)	47	1.71 (1.18, 2.49)	
P for trend				0.78		0.07		0.005	

Note: RR=rate ratio; MV=multivariate; CI=confidence interval

[a] Infertility is defined as attempting to become pregnant for >1 year without success. Cases with "no past or concurrent infertility" are women who never reported infertility. Cases with "concurrent infertility" are women who reported an infertility evaluation in the same follow-up cycle as laparoscopic confirmation of endometriosis.

[b] Adjusted for current age (continuous months) and calendar time (2-year questionnaire period).

[c] Adjusted for current age (continuous months), calendar time (2-year questionnaire period), age at menarche (<10, 10, 11, 12, 13, 14, 15, >15), menstrual cycle regularity (very regular, regular, usually regular, always regular, no periods) between ages 18–22, parity (nulliparous, 1, 2, 3, ≥4), oral contraceptive use (never, past, current), body mass index (<19, 19–20.4, 20.5–21.9, 22.0–24.9, 25.0–29.9, ≥30), alcohol consumption (nondrinkers, <5 g/day, 5–9.9 g/day, ≥10 g/day), smoking status (never, former, current), and physical activity (<3, 3–8.9, 9–17.9, 18–26.9, 27–41.9, ≥42 MET-hr/week).

[d] P value, test for heterogeneity comparing the effect of rotating nightshift work among women with no past or current infertility with those with concurrent infertility.

Am J Obstet Gynecol. Author manuscript; available in PMC 2012 November 1.

TABLE 3

Adjusted relative risks (RRs) and 95% confidence intervals (CIs) of endometriosis risk by rotating night shift work in three categories among premenopausal women in the Nurses' Health Study II (1989–2003), excluding permanent night workers.

Duration of rotating night shift	Never infertility work-up				Ever infertility work-up				p[c]
	Cases	Person years	Age-adjusted RR[b]	MV RR (95% CI)[c]	Cases	Person years	Age-adjusted RR[b]	MV RR (95% CI)[c]	
Baseline exposure									
Never	477	288,011	1.00	1.00	344	47,785	1.00	1.00	0.13
1–4.9 years	514	324,807	0.95 (0.84, 1.08)	0.96 (0.85, 1.09)	427	58,234	1.00 (0.86, 1.15)	0.95 (0.82,1.10)	
≥5 years	103	72,056	0.84 (0.68, 1.04)	0.80 (0.64, 0.99)	107	14,198	1.16 (0.93, 1.44)	1.07 (0.85, 1.34)	
P for trend				0.07				0.89	
Cumulative update									
Never	423	254,712	1.00	1.00	308	42,575	1.00	1.00	0.21
1–4.9 years	531	333,346	0.97 (0.86, 1.11)	0.97 (0.86, 1.11)	432	58,726	1.02 (0.87, 1.18)	0.96 (0.82, 1.11)	
≥5 years	140	96,816	0.90 (0.74, 1.09)	0.86 (0.70, 1.04)	138	18,917	1.18 (0.96, 1.45)	1.10 (0.89, 1.36)	
P for trend				0.16				0.60	

Note: RR=rate ratio; MV=multivariate; CI=confidence interval

[a] Adjusted for current age (continuous months) and calendar time (2-year questionnaire period).

[b] Adjusted for current age (continuous months), calendar time (2-year questionnaire period), age at menarche (<10, 10, 11, 12, 13, 14, 15, >15), menstrual cycle regularity (very regular, regular, usually regular, always regular, no periods) between ages 18–22, parity (nulliparous, 1, 2, 3, ≥4), oral contraceptive use (never, past, current), body mass index (<19, 19–20.4, 20.5–21.9, 22.0–24.9, 25.0–29.9, ≥30), alcohol consumption (nondrinkers, <5 g/day, 5–9.9 g/day, ≥10 g/day), smoking status (never, former, current), and physical activity (<3, 3–8.9, 9–17.9, 18–26.9, 27–41.9, ≥42 MET-hr/week).

[c] P value, test for heterogeneity comparing the effect of rotating nightshift work among women who have never reported having had a clinical evaluation for infertility with those who have ever reported having had a clinical infertility evaluation.