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Length of Menstrual Cycle and Risk of Endometriosis

A Meta-Analysis of 11 Case–Control Studies

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Abstract: Endometriosis is a complex disease that affects a large number of women worldwide and may cause pain and infertility.

To systematically review published studies evaluating the relationship between menstrual cycle length and risk of endometriosis.

We searched the Cochrane Library, PubMed, Web of Science, and EMBASE in databases in July 2014 using the keywords ''case–control studies,'' ''epidemiologic determinants,'' ''risk factors,'' ''menstrual cycle,'' ''menstrual length,'' ''menstrual character,'' and ''endometriosis.''

We included case–control studies published in English that investigated cases of surgically confirmed endometriosis and examined the relationship between endometriosis risk and menstrual cycle.

Eleven articles that met the inclusion criteria included data of 3392 women with endometriosis and 5006 controls. Fixed-effects and random-effects models were used for the evaluation.

For the association of risk of endometriosis and menstrual cycle length shorter than or equal to 27 days (SEQ27) or length longer than or equal to 29 days (LEQ29), the odds ratio was 1.22 (95% confidence interval [CI]: 1.05–1.43) and 0.68 (95% CI: 0.48–0.96), respectively.

In conclusion, this meta-analysis suggests that menstrual cycle length SEQ27 increase the risk of endometriosis and cycle length LEQ29 decrease the risk.

(*Medicine* 95(9):e2922)

Abbreviations: BMI = body mass index, CI = confidence interval, IGF-1 = insulin like growth factor 1, LEQ29 = longer than or equal to 29 days, NOS = Newcastle–Ottawa Scale, OR = odds ratio, SE = standard error, SEQ27 = shorter than or equal to 27 days, VEGF = vascular endothelial growth factor.

INTRODUCTION

Endometriosis is a complex gynecologic disorder characterized by benign proliferation of ectopic endometrial glands and stroma in the peritoneal cavity, with dysmenorrhea, pelvic pain, and infertility being typical symptoms.[1,2] It affects approximately 10% to 15% of women of reproductive age and as many as 50% of women with infertility.[3]

Genetic predisposition and environmental factors are considered to be closely associated with the development of endometriosis.[4–7] However, the pathogenesis of this disease is currently not very clear. Three main theories used to explain the manifestations and invasion are the retrograde menstruation theory, Müllerian metaplasia theory, and lymphatic spread theory.[8]

Many studies have surveyed the risk factors associated with the disease. It has been shown that age, race, body mass index, alcohol usage, cigarette smoking, and menstrual characters (such as the length and regularity of menstrual cycles, intensity of menstrual flow, and dysmenorrhea) are associated with the incidence of endometriosis.[9–12]

Menstrual cycle characteristics affecting the frequency of exposure to menstruation may be related to the incidence of endometriosis.[13] Thus, several observational studies and a meta-analysis have provided some evidence that early age at menarche increases the risk of endometriosis.[14,15] The length of the menstrual cycle varies greatly among women (ranging from 21 to 35 days), with 28 days designated as the average length.[16] Accordingly, 28 days was used as the cut-off value for group assignment in a number of studies relevant to endometriosis.[17–22] We placed demarcation points at 27 and 29 days and defined menstrual cycle length shorter than or equal to 27 days as SEQ27 and longer than or equal to 29 days as LEQ29. The majority of observational studies have examined the relationship between menstrual cycle length, 1 of the menstrual characteristics, and endometriosis, and some have found an association between a shorter menstrual cycle and the incidence of this disease.[20–23] On the contrary, Sangi-Haghpeykar's study[24] showed that women with long cycle lengths were 1.8 times more likely to develop endometriosis than those with short cycle lengths. Dramatically, some studies[11,23,25] did not find any significant correlation between short menstrual cycle length and endometriosis at all. Therefore, the association between menstrual cycle length and endometriosis needs further confirmed. The aim of the present study is to perform a meta-analysis to examine the association between menstrual cycle length and endometriosis.

METHODS

Search Strategy

A systematic search was performed in the Cochrane Library, PubMed, MEDLINE, and EMBASE databases for all case–control studies published between January 1993 and July 2014 using the following keywords: ''Case–control studies,'' ''epidemiologic determinants,'' ''risk factors,''

"menstrual cycle," "menstrual length," "menstrual character," and "endometriosis." Reference lists of selected publications were then searched manually by 1 of the authors to identify additional relevant studies. Two authors reviewed the papers and independently selected eligible articles for the systematic review.

Study Selection

Studies were included if they investigated cases of surgically confirmed endometriosis; examined the relationship between endometriosis risk and menstrual cycle; were case–control studies; and were full-length articles published in English. Only original publications were included; conference abstracts and dissertations were excluded.

Data Extraction and Quality Assessment

Data were extracted independently by 2 investigators, and discrepancies were resolved by discussion. The following details were collected: first author's last name, year of publication, country of origin, study design, number of subjects, age, length of menstrual cycle in days, and odds ratios (ORs) of endometriosis and corresponding confidence intervals (CIs). The quality of primary studies was evaluated using the Newcastle–Ottawa Scale (NOS) according to 3 criteria: participant selection, comparability of study groups, and assessment of exposure.[26]

Statistic Analysis

ORs and 95% CIs for menstrual cycle length and endometriosis were calculated in a random-effects model and a fixed-effects model when appropriate. Both the Cochran Q statistic to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated. A *P* value of more than the nominal level of 0.10 for the Q statistic indicated a lack of heterogeneity across studies, allowing for the use of a fixed-effects model; otherwise, the random-effects model was used. To explore sources of heterogeneity across studies, subgroup analysis was performed. Sensitivity analysis was performed to assess the stability of results. All statistical analyses were performed with the RevMan 5.3 software.

RESULTS

Results of the Literature Search

Of the 631 reports initially identified from the database search, 603 articles were excluded after carefully reviewing the titles and abstracts because of low relevance to the present study (Figure 1). Among the 28 remaining articles, 17 more were excluded after an in-depth examination for the following reasons: 7 were not case–control studies, 7 did not mention menstrual cycle, 2 only presented mean values and not numbers of subjects, and 1 had similarities with 1 of the selected reports. Thus, only 11 studies fulfilled the predefined entry criteria and were ultimately selected for meta-analysis.

Study Characteristics

Table 1 summarizes the 11 case–control studies selected for meta-analysis. Numbers of subjects in the studies published between 1993 and 2014 ranged from 186 to 2777, and there were 3392 cases of surgically diagnosed endometriosis and 5006 controls (Table 1).[18–22,24,25,27–30] Fortunately, we received the original data from one author of study[22] and used them in data analysis. The studies were conducted in Italy (n = 4), the United States (n = 2), Canada (n = 2), Australia
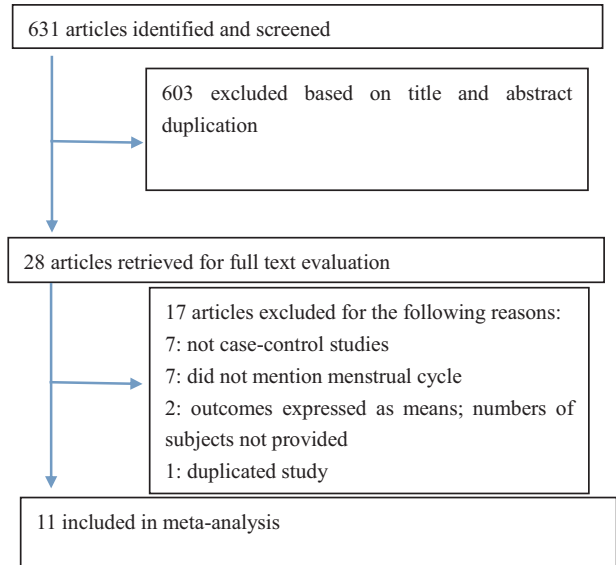

FIGURE 1. Flow diagram illustrating the study selection process.

(n = 1), Malaysia (n = 1), and Iran (n = 1). Subjects were generally younger than 55 years,[18–21,28,29] although women up to 64 years old were included in 1 study.[24] Four studies[22,25,27,30] did not provide the subjects' age explicitly but used age ranges. Reports differed with respect to the description of menstrual cycle. Five studies described menstrual cycle as "regular" or "irregular,"[19,22,27,29,30] and 2 of them did not mention the duration.[29,30] Nine studies[18–22,24,25,27,28] used clearly defined intervals for the menstrual cycle length but the intervals in different studies were not the same. Five studies[18–20,22,25] provided the numbers of women in case and control with the length SEQ27 and 5 studies[19,20,22,24,28] provided the cases numbers with the length LEQ29. Three studies used age-matched controls.[21,28,30] In particular, 1 study[28] utilized age-matched twins as case and control subjects, whereas another[18] employed 2 control groups: 100 controls who were friends of the patients with endometriosis and 98 medical controls (patients from the same medical practice with conditions other than endometriosis).

Data Quality

The quality of the studies was assessed by 2 investigators using the NOS, a validated tool for evaluating observational and nonrandomized studies, and the results were scored from 4 to 8. In particular, 1 study[19] received a score of 8, 2[18,20] a score of 7, 3[21,25,28] a score of 6, 1[24] a score of 5, and the remaining 4[22,27,29,30] a score of 4 (Table 2).

Menstrual Cycle and Risk of Endometriosis

Women with menstrual cycle lengths SEQ27 were at an increased risk of developing endometriosis (OR: 1.22, 95% CI: 1.05–1.43; Figure 2) and those with menstrual cycle lengths LEQ29 were at an approximately 32% lower risk of endometriosis (OR: 0.68, 95% CI: 0.48–0.96; Figure 3).

Heterogeneity Analysis and Sensitivity Analysis

There was heterogeneity among studies in overall comparisons. We assessed all of the comparison models by country,

TABLE 1. Characteristics of the 11 Case–Control Studies Included in the Analysis

No.	Study	Population	Cases	Controls
1	Treloar 2010, Australia[28]	Women ages 18–55 y recruited from a genetic study of endometriosis and the Australian Twin Registry	268 cases with laparoscopically diagnosed moderate/severe endometriosis	244 women from the Australian Twin Registry with no endometriosis diagnosed in earlier twin studies and age-matched to cases
2	Moini 2012, Iran[22]	Infertile women referred for laparoscopy and infertility workup to 2 referral infertility clinics in Tehran, Iran	250 women with pelvic endometriosis (divided into 2 subgroups: stage I/II: 122 and stage III/IV: 128)	153 women with normal pelvis
3	Berube 1998, Canada[20]	Infertile women ages 20–39 y undergoing diagnostic laparoscopy	329 prospectively enrolled cases with laparoscopically diagnosed endometriosis	262 controls with no endometriosis on laparoscopy
4	Parazzini 1999, Italy[27]	817 women with primary or secondary infertility or chronic pelvic pain	345 women (135 with infertility and 210 with pelvic pain)	472 women (258 with infertility and 241 with pelvic pain)
5	Parazzini 1995, Italy[30]	898 women from Lombardy, Northern Italy	376 women with pelvic endometriosis from Lombardy, Northern Italy (stages I, II, III, and IV: 129, 76, 96, and 75, respectively)	522 women admitted to hospital for acute conditions
6	Arumugam 1997, Malaysia[21]	Women ages 19–45 y admitted to gynecology wards in 2 hospitals and undergoing laparoscopy or laparotomy	305 women with laparoscopically diagnosed endometriosis	305 age-matched controls with fibroids, ovarian tumors, ectopic pregnancy, dysfunctional uterine bleeding, pelvic inflammatory disease, and infertility
7	Sangi-Haghpeykar 1995, USA[24]	Multiparous women who underwent laparoscopy for tubal sterilization	126 women with laparoscopically diagnosed endometriosis	504 women with laparoscopically confirmed absence of endometriosis
8	Parazzini 2008, Italy[29]	672 women younger than 55 y old from Italy	Group 1: 181 women with deep endometriosis; group 2: 162 women with endometriosis at other sites	329 women admitted for acute nongynecological, nonhormonal, and non-neoplastic conditions (<55 y old)
9	Hemmings 2004, Canada[25]	Women who underwent surgery for diagnostic laparoscopy, tubal ligation, or hysterectomy	896 cases of surgically diagnosed endometriosis	1881 controls surgically confirmed not to have endometriosis
10	Darrow 1993, USA[18]	Women ages 19–45 y undergoing laparoscopy and their friends	104 prospectively enrolled women with laparoscopically diagnosed endometriosis	100 friend controls and 98 medical controls
11	Signorello 1997, Italy[19]	Infertile women ages 23–44 y scheduled for laparoscopy	50 prospectively enrolled infertile women with laparoscopically diagnosed endometriosis	189 fertile women without endometriosis and 247 infertile women without endometriosis

TABLE 2. Quality of the Included Studies Assessed Using the Newcastle–Ottawa Scale

| No.	Study	Selection				Comparability		Exposure			Total Score
1	Treloar 2010[28]	1	1	0	1	1	1	0	1	0	6
2	Moini 2012[22]	1	1	0	1	0	0	0	1	0	4
3	Berube 1998[20]	1	1	1	1	0	1	1	1	0	7
4	Parazzini 1999[27]	1	1	0	1	0	0	0	1	0	4
5	Parazzini 1995[30]	1	1	0	0	1	1	0	0	0	4
6	Arumugam 1997[21]	1	1	0	1	1	1	0	1	0	6
7	Sangi-Haghpeykar 1995[24]	1	1	0	1	1	0	0	1	0	5
8	Parazzini 2008[29]	1	1	0	1	0	0	0	1	0	4
9	Hemmings 2004[25]	1	0	1	1	0	1	1	1	0	6
10	Darrrow 1993[18]	1	1	1	0	1	1	1	1	0	7
11	Signorello 1997[19]	1	1	1	1	1	1	1	1	0	8
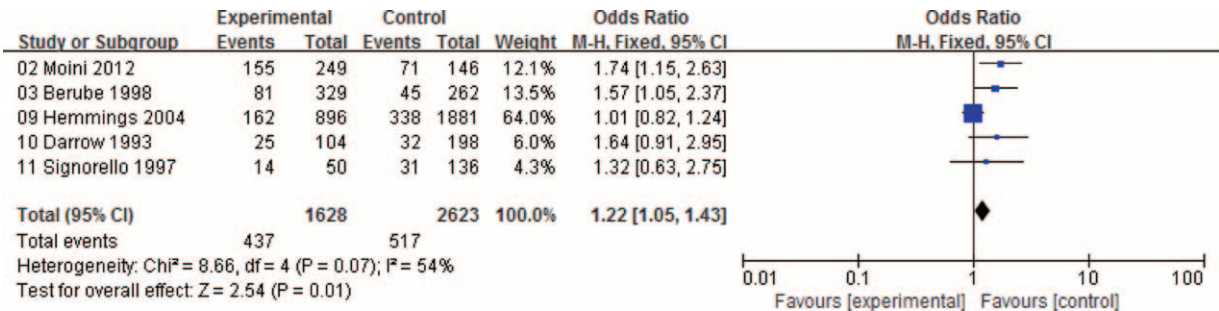
FIGURE 2. Forest plot of ORs with 95% CIs for menstrual cycle length SEQ27 and risk for endometriosis. CI = confidence interval, OR = odds ratio.

and study sample size ($\leq$300 subjects or >300 subjects) to explore sources of heterogeneity across studies. However, none of these variables could explain the heterogeneity. In the sensitivity analysis, we repeat the meta-analysis by omitting each study 1 by 1 to exam the influence of each study on the pooled OR. The result proved that our results were reliable. In addition, when excluding 1 study[24] simultaneously, the I^2 significantly decreased from 79% to 49% which was not so high as before. Therefore, the study[24] was considered as the source of heterogeneity and finally excluded when analyzed.

Publication Bias

Funnel plots for the association between menstrual cycle length SEQ27 or menstrual cycle length LEQ29 and risk for endometriosis were shown in the Figures 4 and 5. Visual inspection of funnel plot asymmetry was conducted to assess the potential publication bias. Obviously, no indication of asymmetry was observed in the funnel plots.

DISCUSSION

The consistency of the results of this meta-analysis indicates that menstrual cycle length SEQ27 is inversely associated with the risk of endometriosis and menstrual cycle length LEQ29 decreases the risk.

The retrograde bleeding hypothesis can be 1 explanation for these findings. Sampson's theory of retrograde menstruation,[31] which is supported by the anatomical distribution of endometriotic implants[32] and higher prevalence of the disease
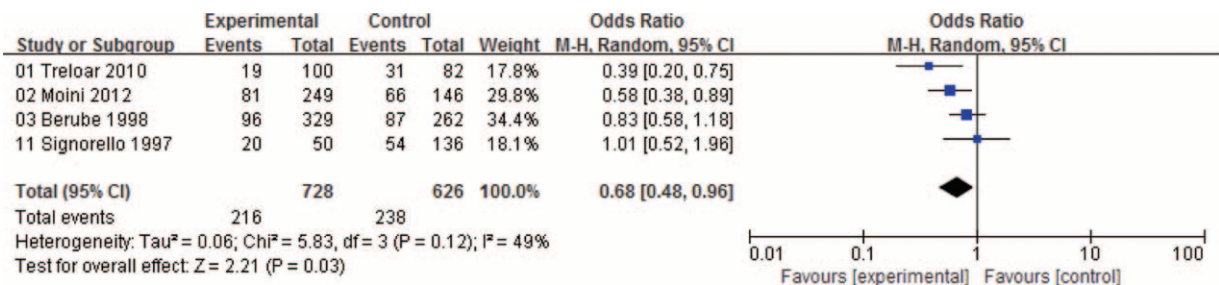

FIGURE 3. Forest plot of ORs with 95% CIs for menstrual cycle length LEQ29 and risk for endometriosis. CI = confidence interval, OR = odds ratio.
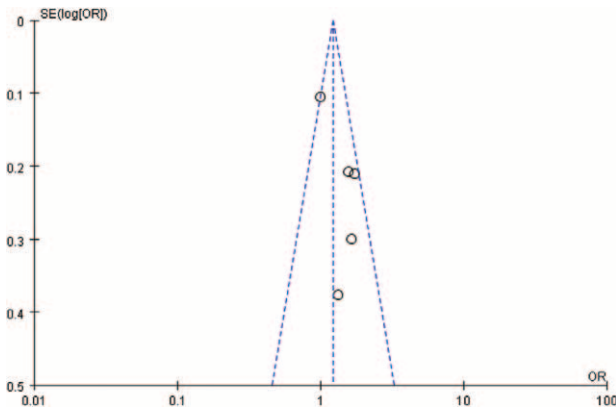
FIGURE 4. Funnel plot for the association between menstrual cycle length SEQ27 and risk for endometriosis.

in women with obstructive Müllerian anomalies, is currently considered to describe the main causal mechanism of endometriosis.[15,33] A short menstrual cycle usually means an increased menstrual frequency and higher risk of exposure to menstruation. Menstrual cycle length SEQ27, which is shorter than average cycle length, could potentially increase the frequency and the risk of retrograde bleeding and finally increase the incidence of endometriosis. However, the cycle length LEQ29 influences the endometriosis in a contrary way.

The other potential explanation for our study results may be the fact that endometrial-like tissues of short-cycle-length (SEQ27) women are at a relatively higher frequency of exposure to higher levels of estrogen than that of long-cycle-length women. Several studies have already found that the ectopic growth of endometrial-like tissue was depended upon sex steroid hormones[34] and local growth factors[35] such as insulin-like growth factor 1 (IGF-1)[36] or vascular endothelial growth factor (VEGF).[37] Commonly, short cycle length comes along with punctually ovulation and the estrogen level sharply increasing in a short period of time before ovulation. Estrogen has synergistic effects with IGF-1/VEGF and sometimes enhance the effects of IGF-1/VEGF on ectopic endometrial cells proliferation and mitosis,[38] which possibly ended with endometriosis.

Consistent with our conclusion, some studies[20–23] concluded that short menstrual cycle length increases the risk of
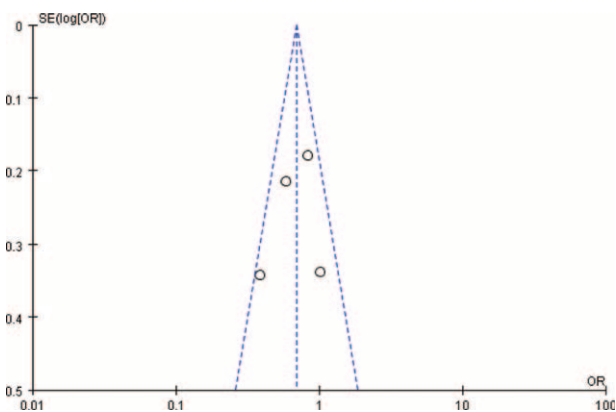

FIGURE 5. Funnel plot for the association between menstrual cycle length LEQ29 and risk for endometriosis.

endometriosis. Oppositely, Sangi-Haghpeykar's study[24] draw a conclusion that long cycle length is a risk factor. The opposite conclusion may result from the differences in the subjects' source population, race, geographical region, and age. In summary, findings of our study can be used to guide the diagnostic and therapeutic strategies of endometriosis in clinical practices. For instance, the artificial menstrual cycle can be tried to manage the development of endometriosis in terms of delaying the menstruation or ovulatory phase. There are some limitations in our studies: only studies published in English between 1993 and 2014 were included; and the number of included studies and the total sample size were relatively small. More well-designed studies should be conducted.

CONCLUSIONS

In conclusion, this meta-analysis suggests that menstrual cycle length SEQ27 increase the risk of endometriosis and length LEQ29 decrease the risk.

ACKNOWLEDGMENTS

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