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SYSTEMATIC REVIEW – OPEN ACCESS

The Association Between Parity and the Risk of Endometriosis: A Meta-Analysis

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ABSTRACT

Objective: Studies regarding the effect of parity on endometriosis are in controversy. This study is the first, to our knowledge, to evaluate the association between parity and risk of endometriosis. The purpose of performing this meta-analysis was evaluating the association between parity and risk of endometriosis.

Materials and Methods: We conducted an advanced search in PubMed, Scopus, and Web of Science to explore data from the beginning of 2000. We performed Egger's and Begg's tests to evaluate publication bias. The Q-statistic test and I-squared (I^2) test were used to estimate the heterogeneity among studies. The association between parity and risk of endometriosis was determined by the random effects model.

Results: In total, we included 17 studies in the present meta-analysis with 78,644 subjects. The pooled overall OR was 0.53 (95% CI: 0.40, 0.67). The significant heterogeneity was observed among these studies (I^2=95.7%, p<0.001).

Conclusion: The present study is the first meta-analysis that showed that parity is a protective factor for endometriosis. In addition, the risk of endometriosis decreased with higher parity based on subgroup analysis.

Keywords: Endometriosis, meta-analysis, parity, pregnancy

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INTRODUCTION

Endometriosis is defined as the benign proliferation of functioning of endometrial glands and stroma in the presence endometrial tissue outside of the uterine cavity. Endometriosis is a symptomatic disease and its prevalence is 10% in reproductive age. The endometriosis is one of the most benign diseases estrogen dependent in the gynecology field as well as a source of economic burden in the field of health (1).

The studies suggest that women with endometriosis are in relation to the increase of the risk for other diseases such as fibromyalgia, rheumatoid arthritis, and ovarian cancer (2).

The endometriosis symptoms are dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. The etiology and molecular mechanisms of endometriosis are not unknown (3) and few risk factors have been identified (4).

Among the risk factors identified, some studies have examined the role of higher socioeconomic status, low body mass index, lean women, early menarche, short length of menstrual cycle, race, heavy metals, alcohol, and caffeine use (5–7).

The studies regarding the effect of parity on endometriosis are in controversy. Some studies confirmed this association (3, 8, 9) and others not (10–12).

This study is the first, to our knowledge, to evaluate the association between parity and risk of endometriosis. The purpose of performing this meta-analysis was evaluating the association between parity and risk of endometriosis.

MATERIALS and METHODS

Data Extraction

Two authors (SK and EJ) reviewed all studies independently and we had not restriction for the maternal age, design of studies, geographic region, and language of papers.

Sources

The meta-analysis was carried out based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis. We conducted an advanced search in PubMed, Scopus, and Web of Science to explore data from the beginning of 2000. The search terms included were endometriosis and parity. Furthermore, the references of the included literature were searched manually.

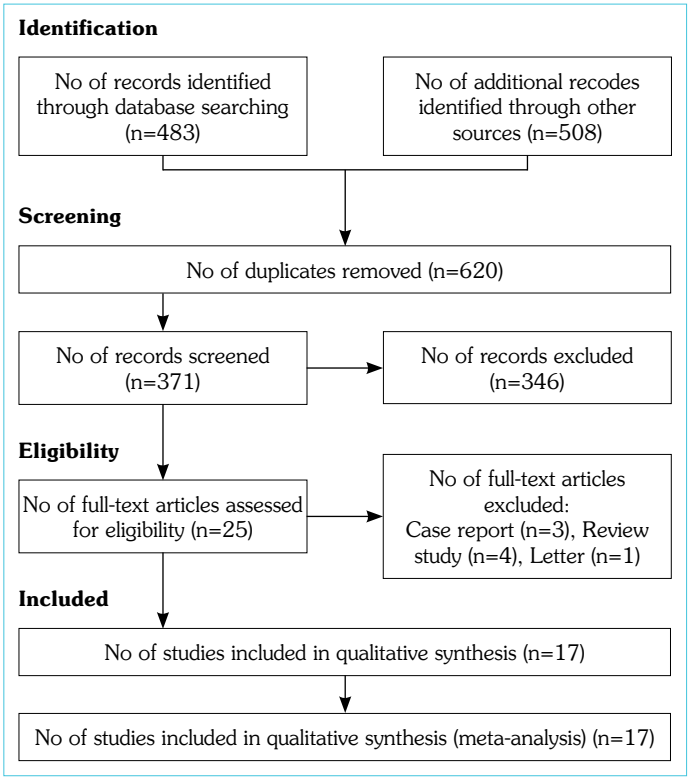

Figure 1. Flow of information through the different phases of the systematic review

Criteria for Included Studies

The association between parity and risk of endometriosis in epidemiological studies (case control, cohort, and cross sectional) was included without limitation of age, race, country, and language of papers. We included studies from the year of 2000 until December 2019. The exposure and outcome of interest were parity and endometriosis, respectively.

Quality Assessment of the Eligible Studies

The Newcastle-Ottawa scale (NOS), a nine-star system, was used for evaluating the quality of studies (13). In this scale, the range of the score is 0–9. It has three sections (election, comparability, and exposure). The scores of 0–6 and 7–9 were studies with low quality and high quality, respectively.

Statistical Analysis

We extracted odds ratio (OR) and risk ratio (RR) and their 95% confidence intervals (CIs) from the included studies. The Q-statistic test and I-squared (I^2) test were used to estimate the heterogeneity among studies (14). The association between parity and risk of endometriosis was determined by the random effects model. We performed Egger's and Begg's tests to evaluate publication bias (15). All analyses were conducted in the Stata software, version 14 (StataCorp, College Station, TX, USA).

Subgroup Analysis

Subgroup analyses based on the number of parity and the design of studies were performed to assess the confounders in this meta-analysis.

RESULTS

Description of Studies

The electronic search is presented in Figure 1. The full papers of the 25 selected studies were included for detailed assessment. Eight of these studies were removed due to not having inclusion criteria. In total, 17 studies were remained in the present meta-analysis

Table 1. Summary results of the included studies

1st author, year	Country	Design	Sample size	Estimate	Adjustment	Age (mean)	Quality
Saha et al., 2017	Sweden	Cross sectional	28,822	OR	Adjusted	No data	High
Saraswat et al., 2016	Scotland	Cohort	13,655	OR	Crude	29.5	High
Upson et al., 2015	USA	Case control	473	OR	Crude	18–49	High
Zanetta et al., 2000	USA	Case control	89	OR	Crude	46–48	High
Ballard et al., 2008	UK	Case control	26779	OR	Adjusted	15–55	High
Calhaz-Jorge et al., 2004	Portugal	Cohort	661	OR	Crude	30.8	High
Cardoso et al., 2017	Brazil	Case control	2955	OR	Crude	No data	High
Louis et al., 2012	USA	Cohort	471	OR	Crude	No data	High
Marino et al., 2009	USA	Cohort	1040	OR	Crude	18–49	High
Oliveria et al., 2007	Brazil	Case control	111	OR	Adjusted	15–45	High
Rashidi et al., 2017	Iran	Case control	100	OR	Crude	32.7	Low
Fujii et al., 2016	Japan	Cohort	631	OR	Crude	35	High
Ashrafi et al., 2016	Iran	Case control	1282	OR	Crude	32.4	High
Peterson et al., 2013	USA	Cohort	600	OR	Adjusted	21.8	High
Liu et al., 2016	China	Case control	420	OR	Crude	33.1	High
Hediger et al., 2005	USA	Case control	84	OR	Adjusted	32.1	High
Backonja et al., 2017	USA	Cohort	471	OR	Crude	32.8	High

OR: Odds ratio

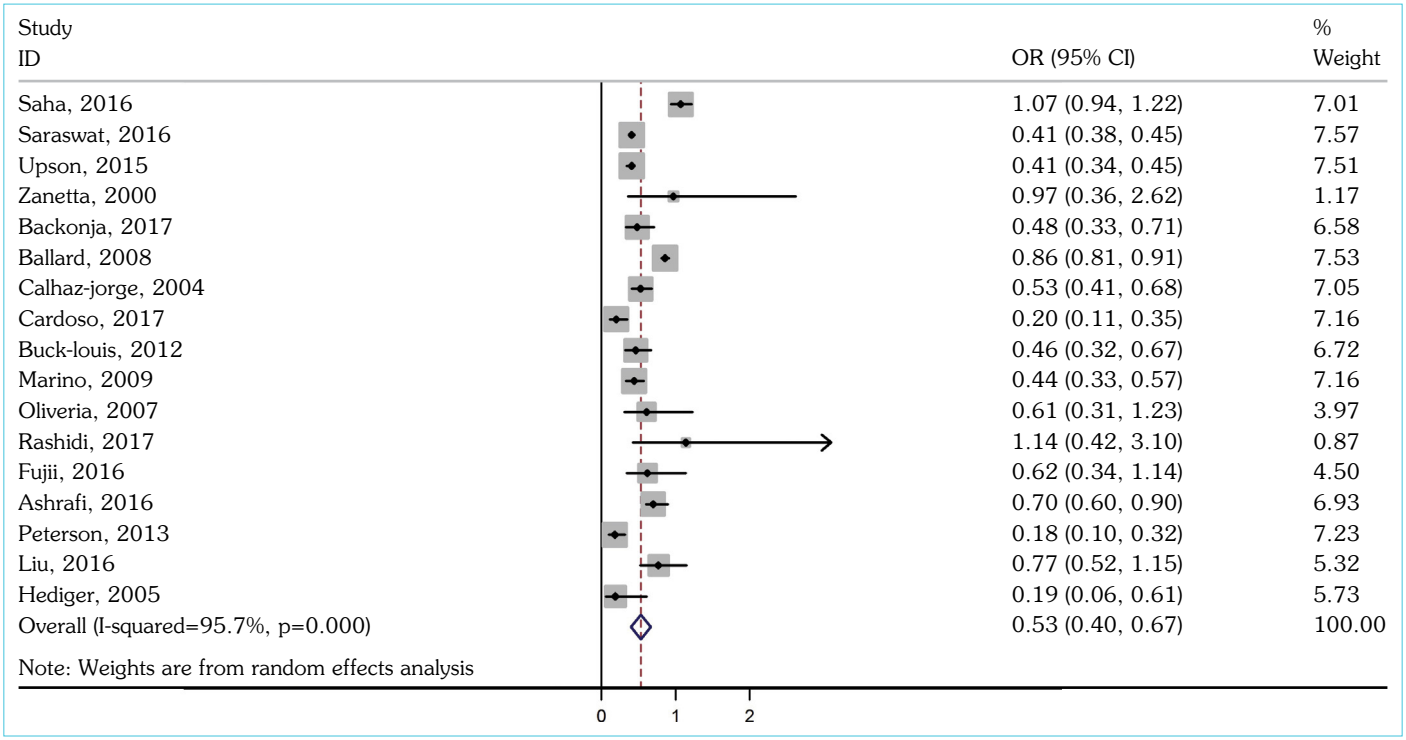

Figure 2. Forest plot of the association between parity and endometriosis

that was published between 2000 and 2017. Of these studies, nine studies case control (3, 6, 9–11, 16–19), seven studies cohort (8, 20–25), and one study cross sectional (12) were with a sample of 78,644 subjects. All the studies were published in English (Table 1).

Only four studies in this meta-analysis were in the adjusted model for confounder variables. The confounder variables of the association between endometriosis and parity were including age, age at menarche, body mass index, oral contraceptive as contraceptive, infertility, coffee, smoking, and alcohol intake (Table 1).

Main Analysis

We reported in Figure 2 pooled ORs from the studies. There was a significant association between parity and endometriosis (OR=0.53, 95% CI=0.40 to 0.67). The significant heterogeneity was observed among these studies (I^2=95.7%, p<0.001). The asymmetry did not observe based on the funnel plot, therefore, there was no publication bias.

The analysis was conducted based on the study design in Figure 3. The pooled OR in case–control studies and in cohort studies had significant association 0.56 (95% CI: 0.33, 0.79) and 0.42 (95% CI: 0.33, 0.51), respectively.

The p values for Begg's and Egger's regression asymmetry test were 0.742 and 0.236 confirmed it, respectively (Fig. 4).

Quality of the Studies

According to the scale of NOS, 16 studies had quality high and three had quality low. The quality of studies is presented in Table 1.

Subgroup Analysis

According to the number of parity in women that have one parity as well as two and more parity compared with nulliparity, OR was 0.77 (95% CI: 0.64, 0.91) and 0.44 (95% CI: 0.15, 0.73), respectively (Table 2).

DISCUSSION

In the present meta-analysis, we carried out the association between parity and endometriosis and identified a significant inverse association between parity and endometriosis. Based on these results, the multiparity compared nulliparity decreased the risk of endometriosis. Furthermore, the risk of endometriosis decreased with parity increase based on subgroup analysis. There was high heterogeneity between nulliparity women compared with multiparity women in this meta-analysis because did not determine the precise number of parity in the studies included. When we conducted subgroup analysis, the heterogeneity decreased in women that have one parity in compared with nulliparity.

Infertility is one of the symptoms of endometriosis. The parity may be explained by the solution of infertility in women with endometriosis who achieve a pregnancy irrespective of the time to pregnancy (26). The mechanism of decreased incidence of endometriosis associated with parity may be due to suppression of endometriosis by the progesterone dominant hormonal milieu (25).

The hypothesis that endometriosis leads to infertility or fecundity decrease is in controversy. It is unknown whether endometriosis and infertility share a common cause or whether infertility is in the etiological pathway to endometriosis (25).

Wu et al. (2015) (27) in a meta-analysis study reported that parity may be associated with a decreased risk of endometrial cancer (RR=0.69, 95% CI [0.65–0.74]). The potential explanation is that at each birth delivery, there is mechanical shedding of malignant/premalignant endometrial cells.

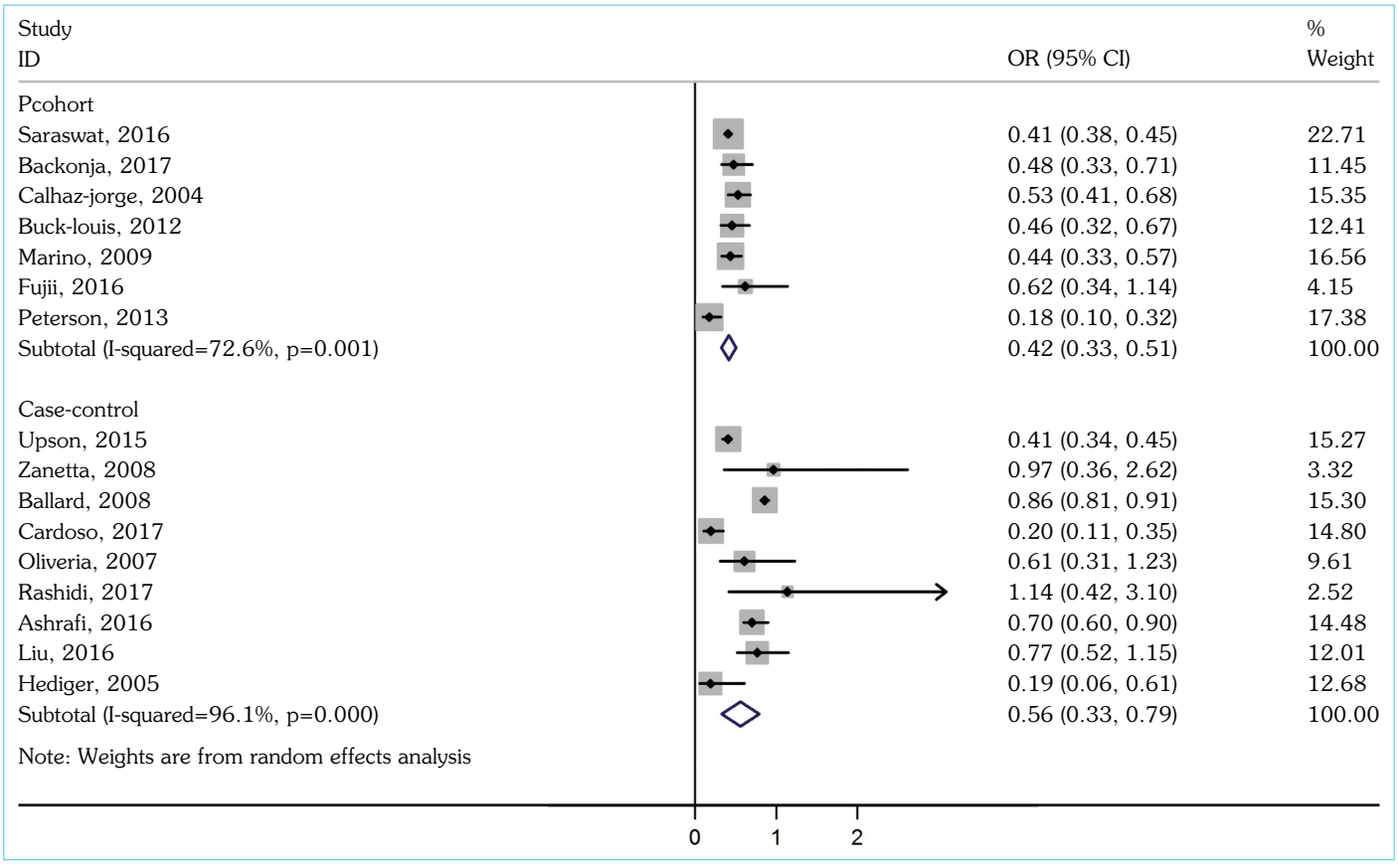

Figure 3. **Forest plot of the association between parity and endometriosis based on case–control and cohort studies**

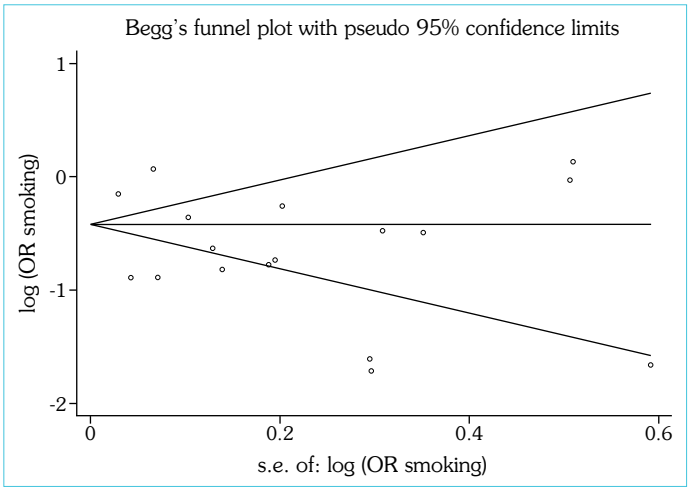

Figure 4. **Funnel plot of the association between parity and endometriosis**

There are some limitations in this meta-analysis. (a) Only four of the studies were performed for adjusted results, so our analyses are more based on the crude form extracted from the studies. (b) We, in this meta-analysis, evaluated only a single parameter (parity), while endometriosis is an equation with many unknowns. Therefore, results are more prone to selection bias. (c) Because of high heterogeneity in the present meta-analysis, we conducted a subgroup analysis based on design studies and number of parity to explore the source of heterogeneity. Although the degree of

Table 2. Results of subgroup analysis of the number of parity on endometriosis

Subgroups	Studies		
Number of parity	**No. of studies**	**OR (95% CI)**	**I^2 (%)**
1	5	0.77 (0.64, 0.91)	15.5
2+	5	0.44 (0.15, 0.73)	94.2

OR: Odds ratio; CI: Confidence interval

I^2 heterogeneity was reduced by subgroup analysis based on one parity compared with nulliparity, other sources of heterogeneity were not checked.

The present study is the first meta-analysis that showed that parity is a protective factor for endometriosis. In the consultation in relation to risk factors and protective factors for endometriosis, help for early screening, detection and prevention of the disease should be performed due to the high prevalence of endometriosis in reproductive age.

CONCLUSIONS

The present study is the first meta-analysis that showed that parity is a protective factor for endometriosis. Furthermore, the risk of endometriosis decreased with higher parity based on subgroup analysis.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – EJ, SK; Design – EJ, SK; Supervision – EJ; Data Collection and/or Processing – BF, SK, EJ; Analysis and/or Interpretation – SK, EJ; Literature Search – BF, EJ; Writing – EJ, SK, BF; Critical Reviews – EJ, SK, BF.

Conflict of Interest: The authors have no conflict of interest to declare.

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