Endometriosis and infertility: a systematic review

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ABSTRACT

Endometriosis is an inflammatory disease that is characterized by the presence of benign endometrial stroma outside the uterine cavity. Endometriosis is considered a major cause of chronic pelvic pain. The correlation between endometriosis and infertility is still elusive, although such an association was clinically recognized.

The present review aimed at assessing the prevalence of endometriosis among infertility and the association between endometriosis and infertility by reviewing the previous studies conducted on this subject. Scientific databases, including PubMed, Elsevier, and Google scholar, were explored to search for articles related to our subject. The keywords involved in the search process were “Endometriosis, Prevalence, Prevalent, Proportion, Infertility, Association, and Correlation.” The inclusion criteria were original English articles published after 2005 that reported the prevalence of endometriosis among infertile women. A total of 1,590 articles were obtained, and only nine articles were eligible and included in the final analysis. A total of 2,487 women were included in the nine studies. The method of assessment of endometriosis was mainly diagnostic laparoscopy.

The prevalence of endometriosis among infertile women ranged between 4.9% and 47%. Endometriosis is a common condition that is highly prevalent among infertile women. Endometriosis was also more prone to be associated with primary infertility.

Keywords: Endometriosis, infertility, prevalence, association.

Introduction

Endometriosis is a chronic inflammatory disorder that is characterized by the presence of benign functional endometrial stroma or glands outside the uterine cavity [1,2]. Endometriosis is the most common benign but significantly metastatic and gynecological condition that affects almost 7%-10% of women of reproductive age, and it is considered the major cause of chronic pelvic pain [3,4]. The pelvis is the most commonly affected region by endometriosis; however, extra-pelvic structures can also be involved [5]. Women with endometriosis mainly suffer from pelvic pain, dyspareunia, and dysmenorrhea [6]. These symptoms can affect the patients, including effects on mental, physical, and social well-being [6]. Infertility is defined as the failure to conceive after 1 year or more of unprotected regular sexual intercourse [7]. The correlation between endometriosis and infertility is still elusive, although such an association was clinically recognized [5]. It was accepted that endometriosis-associated infertility is multifactorial with many complex pathological processes occurring within the ovaries, uterus, and pelvic cavity [5]. It was reported that almost 30%-50% of women suffering endometriosis are infertile, and 25%-50% of infertile women have endometriosis [8]. Moreover, it was demonstrated that infertile women are 6-8 times more prone to have endometriosis compared to fertile ones [9].

There was no previous systematic review that reported the prevalence of endometriosis among infertile women. So, this systematic review was performed to identify the prevalence of endometriosis among women with infertility.
Method and Search Strategy

The designing and writing of this systematic review follow the PRISMA checklist guidance for systematic review and meta-analysis [10]. Electronic databases and scientific websites, including PubMed, Google Scholar, Elsevier, Research Gate, Scopus, and Science Direct, were revised to search for articles related to our subject. Due to a lack of focus on the current subject, we extended the publishing date for studies to be included in the current systematic review to include studies published after 2005 till now. Several keywords were used for searching purposes, including “Endometriosis, Prevalence, Prevalent, Proportion, Infertility, Association, and Correlation.” All the titles produced from this exploration were revised.

Eligibility criteria

The findings were then examined to exclude duplicated findings, and irrelevant articles appeared coincidently in the search process. Also, articles published before 2005 were excluded. The remaining findings were examined for the objective to include articles that reported the prevalence of endometriosis among infertile women and studies that reported the association between endometriosis and infertility, whereas other studies were excluded. Only articles written in the English language were included, and any article written in other languages was excluded. Then the type of study was checked to include only the original articles and exclude other types of articles, such as reviews, systematic reviews, meta-analyses, letters to the editor, and case reports. Finally, articles not available for full-text and articles containing overlapped or incomplete data were excluded. The full description of the search strategy is shown in Figure 1.

Data review and analysis

Stage one in the data review included a preliminary review that included reviewing the abstracts of the included articles to determine the data of interest. Then, the full article was reviewed for data extraction; the extraction of data was performed using an excel sheet and then the collected data was reviewed. Finally, the reviewed data was transferred to a pre-designed table for summarization.

Results

This systematic review included nine studies that met the eligible criteria [11-19] (Table 1). The studies were published between 2009 and 2020; there were four studies published in 2020 [11-14], one study published in 2018 [15], one study in 2017 [16], two studies in 2015 [17,18], and one study in 2009 [19]. Regarding the study design, there were two prospective studies [11,13], two descriptive cross-sectional [12,16], one cross-sectional registry-based retrospective and descriptive study [14], one patients series design [15], two retrospective [17,18], and retrospective case series [19]. The total number of participants in the included studies was 2,487; there were eight studies that referred to the inclusion of infertile women with a total number of 1,980 infertile women [11,13,14,15-19], whereas only one referred participants only with a total number of 507 women [12]. The age of women was not stated in the total population in two studies [13,19], whereas the remaining seven studies reported the age of women [11,12,14,15-18]; of those studies, there was one study reported the mean age 30.3 ± 4.1 years [17], whereas six studies reported the age range [11,12,14,15,16,18], and the age range was from 18 years [11] to 43 years [15].

The method of assessment and diagnosis of endometriosis was diagnostic laparoscopy, as reported in the majority of studies [11,13,15-18], whereas one study reported self-administered questionnaire to investigate the presence of endometriosis of women [12], another study reported coelioscopy [14], and the last study reported hysterolaparoscopy [18]. There were five studies reported using the revised American Fertility Society (RAFS) classification for the staging of endometriosis [11,15,16,18,19], whereas the remaining four studies did not report using any classification [12-14, 17].

The prevalence of endometriosis ranged between 4.9% [17] and 47%[19]. The most reported regions with endometriosis were reported in three studies [11,13,14] and included ovaries (100%) [11], (14.4%) [13], (35.7%) [14], Pouch of Douglas (POD) (39.13%) [11], (20.2%) [13], uterine walls (13.04%) [11], (12.5%) [13], uterine ligaments (8.7%) [11], (4.8%) [13], fallopian (39.3%), and pelvic (25%) [14].

There were five studies that reported the stages of endometriosis [13,15,16,18,19], and there was one study that reported the severity of endometriosis regarding infertility type [13].

There were six studies reported the prevalence of primary and secondary endometriosis among patients with endometriosis [11,13,14,17,18,19]; the prevalence of primary infertility ranged between 53.5% [14] and 78.26% [11], whereas the prevalence of secondary infertility among patients of endometriosis ranged between 21.74% [11] and 33.3%[17]. There was one study that reported the association between endometriosis and primary infertility (p = 0.001) [19]. On the other hand, another study reported no association between endometriosis and the type of infertility (p = 0.7) [16]. There were four studies reported the association between endometriosis and age [11,15,16,19], where endometriosis was more common among the age group 26-30 years (47.83%) as reported in one study [11]. Another study reported that endometriosis showed the highest prevalence among the age group 25-35 years old [15]. The third study reported that endometriosis was associated significantly with the age group 24-40 years (p = 0.005) [19]. On the other hand, one study reported no association between endometriosis and the age group (p = 0.8) [16].
Figure 1. Planning of eligible criteria.

Table 1. Summary of the included studies.

<table>
<thead>
<tr>
<th>Author and publication year</th>
<th>Study design</th>
<th>Sample size and age of participants</th>
<th>Method of assessment/staging</th>
<th>Results and main findings</th>
</tr>
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</table>
| Sharfuddin et al. [11]      | Prospective        | - N = 200 infertile women - Age = 18-40 years | - Diagnostic laparoscopy - Staging based on RAFS classification | * The prevalence of endometriosis was 11.5%  
* Of the patients with endometriosis, 78.26% had primary infertility, whereas 21.74% had secondary infertility  
* The sites of endometriosis were ovaries in all cases (100%), POD (39.13%), uterine walls (13.04), uterine ligaments (8.7%)  
* The most commonly affected age group was between 26 and 30 years (47.83%). |
| Khadawardi [12]             | Descriptive cross-sectional | - N = 507 participants - Age = <21-40 years | - Self-administered questionnaire ------- | * The prevalence of endometriosis was 10.7% and the prevalence of infertility was 23.3%  
* There was a significant correlation between endometriosis and infertility (p = 0.025). |

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</table>
| Thakral et al. [13]         | Hospital-based prospective | - N = 104 infertile women - Age=--------- | Diagnostic laparoscopy       | * The prevalence of endometriosis was 30.8%  
* There were 68.8% of patients with endometriosis had primary infertility, whereas 31.2% had secondary infertility  
* Participants with primary infertility belonged to the stage III (34.3%) followed by stage I (21.8%), stage II (9.3%), and stage IV (3.1%).  
* Participants with secondary infertility belonged to stage I (12.5%), followed by stage IV (9.3%), stage II (6.25%), and stage III (3.1%).  
* The site of endometriosis was POD (20.2%), ovaries (14.4%), uterus (12.5), and uterosacral ligament (4.8%)  
* Endometriosis in infertile females is very common |
| Minko et al. [14]           | Cross-sectional registry-based retrospective and descriptive | - N = 166 infertile women - Age = 20-42 years | Coelioscopy ..... ----- | * The prevalence of endometriosis was 33.7%, and the annual incidence of 3.7  
* The fallopian form (39.3%), the ovarian (35.7%), and the pelvic forms (25%)  
* 25% of these patients were asymptomatic and 46.4% showed an infertility period of 4 to 6 years, and 53.5% of the patients presented primary infertility.  
* Endometriosis is a condition diagnosed in most women consulting for infertility |
| Alsarraj [15]               | Patient series | - N = 477 infertile women - Age = 21-43 years | Laparoscopy - Staging based on RAFS classification | * The prevalence of endometriosis was 7.7%  
* There was 67.56% had mild endometriosis, 16.22% had moderate endometriosis, and 16.22% had severe endometriosis  
* The prevalence of endometriosis confirmed by Laparoscopy was greatest among women between 25 and 35 years old  
* The study revealed that a significant number of infertile women have endometriosis |
| Zubair et al. [16]          | Descriptive cross-sectional | - N = 50 infertile and subfertile women - Age = 20-40 years | Laparoscopy - Staging based on RAFS classification | * The prevalence of endometriosis was 20%  
* There were 20% had mild, 40% had moderate, 20% had severe, and 20% had extensive endometriosis  
* There was no significant association between endometriosis with age groups (p = 0.8), or type of infertility (p = 0.7) |
| Ikechebelu et al. [17]      | Retrospective survey | - N = 490 infertile women - Age = mean 30.3 ± 4.1 years | Laparoscopy | * The prevalence of endometriosis was 4.9%  
* There were 66.6% of endometriotic women had primary infertility, and 33.3% had secondary infertility  
* Endometriosis is an important common gynecological problem among infertile women seen at laparoscopy |
| Mishra et al. [18]          | Retrospective | - N = 372 infertile women - Age = 19-40 years | Hysteroscopy - Staging based on RAFS classification | * The prevalence of endometriosis was 43.38%  
* There were 75% of endometriotic women had primary infertility, and 25% had secondary infertility  
* There were 66.1% had mild, 21.66% had moderate, 6.11% had severe, and 6.11% had extensive endometriosis  
* Endometriosis amongst infertile women is increasingly being detected due to the greater use of laparoscopy in the evaluation of infertility |

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Results and main findings

- The prevalence of endometriosis was 47% among women with endometriosis and suffered primary infertility compared to those with endometriosis and suffered secondary infertility (30%).
- Compared to patients without endometriosis, primary infertility was significantly higher among patients with endometriosis (p = 0.001).
- Endometriosis was associated with the age of 24-40 years (p = 0.005).

Discussion

Endometriosis is an inflammatory and chronic disorder among women of reproductive age and can cause infertility and pain [20]. Endometriosis is still the most commonly diagnosed condition among infertile women performing laparoscopy, contributing to the perception of causality [5]. In this systematic review, the majority of studies reported diagnostic laparoscopy for the assessment and diagnosis of endometriosis among women. The incidence of endometriosis among females of reproductive age ranges between 2% and 10%, with a higher prevalence among infertile women [5]. Almost 25%-40% of women suffering from infertility also have endometriosis [21]. In the current analysis, the prevalence of endometriosis among infertile women was high, and it ranged between 4.9% and 47%. Additionally, the prevalence ranged between 20%, and 47% in five studies [13,14,16,18,19]. The prevalence of endometriosis was identified through a systematic review by the inclusion of 11 studies that reported the prevalence of endometriosis in the general population. It was demonstrated that the reported prevalence ranged between 0.8% and 28.6%, with an overall evaluation of 4.4%. Furthermore, the pooled prevalence of endometriosis among infertile women was 23.8% [22]. In our analysis, the mean prevalence of endometriosis among infertile women was similar to the findings of the previous systematic review [22]. We found that the mean endometriosis prevalence among infertile women was 23.29%.

Additionally, we found that endometriosis was more associated with primary infertility compared to secondary infertility. Moreover, higher proportions of women with endometriosis suffered primary infertility, with proportions ranging between 53.5% and 78.26% compared to those with endometriosis and suffered secondary infertility (21.74%-33.3%). Only one study in our analysis supported and reported a significant association between endometriosis and primary infertility (p = 0.001) [19]. However, the other studies reported higher proportions of primary infertility among women with endometriosis. Primary infertility refers that women who have never got pregnant before, and the high proportions of primary infertility among endometriotic women and the association may indicate that endometriosis is a potential cause of primary infertility.

On the other hand, one study in our analysis showed that there was no association between endometriosis and the type of infertility (p = 0.7) [16]. These may be elusive findings, as the studies reported higher proportions of primary infertility among women with endometriosis but didn’t investigate the correlation.

Another risk factor of endometriosis reported in the included studies was the age of women. One out of four studies in our analysis reported a significant association between endometriosis and age groups (p = 0.005) [19], and the three studies reported a high prevalence of endometriosis among certain age groups [11,15,19]. However, each study reported a different age group. Furthermore, one study reported no association between endometriosis and age (p = 0.8) [16].

In a previous large cohort study on women of reproductive age, the risk of infertility was found to be increased by two-fold among women younger than 35 years with endometriosis compared to women without endometriosis [23]. In our analysis, endometriosis was more prevalent among infertile women with age groups of 26-30 years [11], 25-35 years [15], and 24-40 years [19]. However, the studies didn’t perform multivariate analysis.

Women older than 35 years undergo a rapid depletion of their oocyte quality and ovarian reserve in combination with other risk factors, becoming more prominent causes of infertility [24]. This may explain the variation in the age groups reported in our analysis, as women may have experienced other risk factors for infertility and they were additionally suffering endometriosis. However, no additional data regarding risk factors of infertility among such women was reported by the authors. Ovarian endometrioma refers to the growth of ectopic endometrial tissue within the ovary [25]. In the current systematic review, we found that ovaries were the most affected.
organ by endometriosis, followed by POD. The exact pathology of endometriosis-related to infertility is still unclear [26]. Infertility related to endometriosis is multifactorial, with many complex pathophysiology [5]. Fertility can be affected by endometriosis directly by distorting tubo-ovarian anatomy or indirectly by the inflammatory effect and oxidative damage on the oocytes leading to poorer quality oocytes [26].

Furthermore, endometriosis can lead to infertility in moderate to severe cases [27], whereas the association between minimal stages with infertility is still unclear [28]. Based on the American Society of Reproductive Medicine, the association between infertility and endometriosis in moderate to severe disease (stages III-IV) has been linked to severe pelvic adhesions. These adhesions can result in a variety of anatomical abnormalities, such as large ovarian cysts, which can block ovum capture and transport [28-31]. Also, the presence of such endometrial lesions can reduce the rates of implantation and pregnancy rates in assisted reproductive technologies and reduce retrieval rates of the oocyte [28].

In our analysis, mild and moderate stages (minimal stages) were more reported among fertile women, whereas advanced stages (severe and extensive) were less reported among women in the included studies. These findings are in contrast to the previous explanation that infertility is associated with advanced stages of endometriosis. However, none of the studies included in our analysis evaluated the association between the stages of endometriosis and infertility.

In the minimal stage of endometriosis, the association between endometriosis and infertility isn’t evident, as pelvic adhesions aren’t severe enough to generate damage. However, various suggested mechanisms can explain infertility in mild endometriosis, such as defective implantation, eutopic endometrium abnormalities, impaired folliculogenesis, abnormal immunological peritoneal environment, and luteal phase problems [32-34].

### Conclusion
Endometriosis is commonly prevalent among infertile women, and sometimes it is highly prevalent. Furthermore, endometriosis was more prone to be associated with primary infertility rather than secondary infertility. The advanced stages of endometriosis in the current analysis didn’t show an association with infertility. Additionally, age showed elusive findings regarding its correlation with endometriosis.

However, the lack of multivariate analysis in the included studies made it difficult to precisely determine and report different correlations, such as correlations between endometriosis and age, as well as endometriosis stages and infertility. Therefore, further studies are required and recommended to involve multivariate analysis as well as the investigation of the correlation between endometriosis and infertility, not just reporting the prevalence.

### List of Abbreviations
- **POD**: Pouch of Douglas
- **RAFS**: Revised American fertility society

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