Psychosocial Risk Factors for Depression Among Women with Endometriosis

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Abstract

Endometriosis is a complex gynaecological condition affecting approximately 2-17% of women. The abnormal growth of endometrial tissue outside the uterus often results in chronic pelvic pain, dysmenorrhoea, dyspareunia, fatigue and infertility. Several theories attempt to explain the aetiology of endometriosis, but its exact origin remains incomplete. Treatments aid in supressing symptoms but no cure is currently available. Endometriosis has significant psychosocial impact on women, leaving them susceptible to poor mental health and reduced quality of life. This review will explore the aetiology, symptoms and treatments for endometriosis, and discuss the impact of endometriosis on the psychosocial wellbeing of affected women.

Introduction

Endometriosis is an estrogen-dependent, chronic inflammatory gynaecological condition that affects women of reproductive age (Kennedy et al., 2005). It is characterised by endometrial tissue (cells lining the uterus) growing outside the uterus (Eriksen et al., 2008; Giudice, 2010; Kennedy et al., 2005). This abnormal growth can be found anywhere in the body, however, the most common locations are on the pelvic peritoneum, ovaries, and rectovaginal septum (Giudice, 2010). Rarer sites include the diaphragm, pleura, and pericardium (Giudice, 2010). Classic presentation of endometriosis includes chronic pelvic pain, fatigue, dysmenorrhoea (menstrual pain), heavy menstrual bleeding, dyspareunia (painful intercourse) and infertility (Laganà et al., 2017; Pope, Sharma, Sharma, & Mazmanian, 2015). The prevalence of endometriosis is difficult to determine because definitive diagnosis can only be established using laparoscopy (Pope et al., 2015). However, based on community prevalence of symptoms, endometriosis has been estimated to affect between 2% and 17% of the female population (Bernuit et al., 2011; Culley et al., 2013), totalling approximately 176 million women worldwide (Adamson, Kennedy, & Hummelshoj, 2010). The precise aetiology of endometriosis remains unknown, making diagnosis difficult. As a result, endometriosis is often associated with diagnostic delay, leading to frustration, which in turn contributes to poorer mental health and reduced quality of life in affected women (Sepulcri & do Amaral, 2009). Endometriosis is incurable with available treatments focusing on symptom management, especially pain reduction. Studies demonstrate a considerable adverse impact of endometriosis on women's quality of life and psychological wellbeing, with pain playing a central role (Facchin et al., 2015; Lorençatto, Alberto Petta, José Navarro, Bahamondes, & Matos, 2006).

Endometriosis is not only a burden for the individual woman affected but also presents as a burden for society in economic terms. Endometriosis is associated with

substantial indirect and direct economic costs (Simoens et al., 2012). The annual healthcare expenditure in relation to endometriosis is comparable to other significant health conditions such as diabetes, Crohn's disease and rheumatoid arthritis (Marinho et al., 2018; Simoens et al., 2012). On average, the annual cost of endometriosis has been estimated to be €9579 per woman (95% CI: €8559-€10599; (Simoens et al., 2012)) when both direct and indirect costs are considered. The indirect costs of productivity loss account for more than half of the costs at €6298 (Simoens et al., 2012). The direct costs are comprised of health care costs and non-health care costs. Surgery is the most expensive item among health care costs (29% of health care costs), while medication constitutes 10% of health care costs (Simoens et al., 2012).

To better appreciate the extent to which endometriosis affects women, it is beneficial to understand the medical aspects of endometriosis. Thus, the first part of this review will explore the diagnosis of endometriosis, some of the theories that attempt to explain its origin, treatment options, and the physical symptomatic presentation of endometriosis. The second part will review the literature on the impact of endometriosis on mental health, specifically depression and anxiety, intimate relationships, education and employment, and quality of life. Finally, suggestions for future research will be discussed.

Diagnosis and Classification of Endometriosis

The diagnostic gold standard for endometriosis is laparoscopic visualisation (Hsu, Khachikyan, & Stratton, 2010). The revised endometriosis classification system of the American Society for Reproductive Medicine is widely utilised to determine disease stage (Stage I: minimal disease - Stage IV: severe disease) based on type, location, appearance and depth of lesion invasion (American Society for Reproductive Medicine, 1997; Giudice, 2010). Even though staging of endometriosis is useful for determining disease burden and treatment, stages and locations of endometriosis do not correlate with pain severity, nor can they predict response to treatment for pain or infertility (Giudice, 2010; Lorençatto et al.,

2006). This means that women with mild endometriosis may present with intense pelvic pain and women with severe endometriosis may experience less or no pelvic pain (Eriksen et al., 2008; Laganà et al., 2017). Women with endometriosis often experience a significant delay between the onset of symptoms and the final diagnosis of endometriosis (Bernuit et al., 2011; Fourquet et al., 2010; Nnoaham et al., 2011; Sepulcri & do Amaral, 2009), ranging from five (Sepulcri & do Amaral, 2009) to nearly nine years (Fourquet et al., 2010). The delay occurs at both patient and primary health care levels (Ballard, Lowton, & Wright, 2006). At the patient level, women have been found to delay seeking medical assistance. On average, it takes women 3.8 years to seek medical assistance once they experience symptom onset (Cox, Henderson, Andersen, Cagliarini, & Ski, 2003). Various factors have been proposed to explain why women fail to seek early medical assistance. Women may struggle to distinguish between normal and pathological symptoms, they may consider themselves "unlucky" rather than "unwell", and they may fear embarrassment and being perceived as weak (Ballard et al., 2006; Cox et al., 2003). In addition, the perception of menstrual irregularities and pain as "normal" also contributes to women's delay in help-seeking behaviour (Ballard et al., 2006; Cox et al., 2003).

Delays also occur at the primary health care level with time between help-seeking and diagnosis lasting up to 5.7 years (Elaine Denny & Mann, 2008). Primary health care professionals may be reluctant to refer women for further investigation, leading to delay in formal diagnosis (Elaine Denny & Mann, 2008; Nnoaham et al., 2011). Women report an average of seven visits to primary care before obtaining a specialist referral (Nnoaham et al., 2011). Research suggests that women frequently experience normalisation of symptoms, and symptoms being dismissed and/or trivialised during their repeated consultations with doctors (Ballard et al., 2006; Elaine Denny & Mann, 2008). Many women are misdiagnosed, most commonly with irritable bowel syndrome (IBS) and pelvic inflammatory disease, and upon

referral, they are initially referred to incorrect secondary care (Ballard et al., 2006; Elaine Denny & Mann, 2008).

Aetiology of Endometriosis

The aetiology of endometriosis is still unknown. Several theories on the development of endometriosis have been proposed however including theories of retrograde menstruation, coelomic metaplasia, and lymphatic and vascular metastasis. Other potential factors in the pathology of endometriosis include genetics, immunology, and environmental and lifestyle factors. While these major theories have led to the discovery of factors involved in the development of endometriosis, they have been difficult to support and thus remain inconclusive.

Retrograde Menstruation

The theory of retrograde menstruation and implantation (Sampson, 1927) is the most accepted theory of how endometrial tissue makes its way into the peritoneal cavity. The theory suggests that the pathology of endometriosis develops when endometrial tissue is shed from the mucosa of the uterus and migrates back through the fallopian tubes and into the abdomen where it implants and proliferates (Sampson, 1927). Sampson (1927) also proposed that endometrial tissue grows outside of the uterus because the tissue is absorbed into venous circulation during menstruation. Retrograde menstruation occurs in up to 90% of menstruating women (Bokor et al., 2009; Burney & Giudice, 2012); however, not all women with retrograde menstruation have endometriosis (Giudice, 2010). It has been suggested that affected women may have an immune dysfunction that interferes with clearing of the lesions, giving rise to endometriosis (Giudice, 2010).

Coelomic Metaplasia

The theory of coelomic metaplasia includes the potential morphological changes of cells that exist in the ovary. The potential for metaplasia exists because both the ovary and

uterus have cells that derive from the same precursor cell (Vinatier, Orazi, Cosson, & Dufour, 2001). However, some aspects remain unexplained by this theory. First, if the origin of endometriosis is explained by peritoneal metaplasia, then a similar condition ought to be observed in males (Vinatier et al., 2001). Second, coelomic metaplasia would be observed in all tissues derived from coelomic epithelium, including striated and smooth muscle, the heart, the blood and lymphatic vessels, the spleen, kidneys and the adrenal cortex (Ross & Pawlina, 2011). Finally, endometriosis should be more widespread in older women if coelomic metaplasia mirrors usual metaplasia (Ross & Pawlina, 2011).

Lymphatic and Vascular Metastasis

The theory of lymphatic and vascular metastasis (Vinatier et al., 2001) suggests that parts of endometrial tissue are absorbed into lymphatic spaces between muscle bundles of the uterine wall and are transported to superficial lymphatics. This occurs during the invasion of the myometrium by its mucosa (Vinatier et al., 2001). The theory of lymphatic and vascular metastasis potentially explains distant lesions as endometrial tissue is taken up by the blood supply and lymphatic vessels in the uterus and transported to other parts of the body (Giudice, 2010; Vinatier et al., 2001). However, this does not explain the particular location of most endometrial lesions: the surface of the ovaries and within the abdominal peritoneum.

Environmental and Lifestyle Factors

Dietary factors and environmental toxins are potentially linked to the development and progression of endometriosis (Bellelis, Podgaec, & Abrão, 2011; Missmer et al., 2010). Through diet, humans are exposed to environmental toxins that potentially disrupt physiological processes and lead to the development of endometriosis (Bellelis et al., 2011; White & Birnbaum, 2009). Endocrine disruption occurs because environmental toxins alter steroid synthesis or hormone receptor function, disrupt immune function, and inhibit reproductive function by epigenetic modifications (Bruner-Tran, Yeaman, Crispens, Igarashi,

& Osteen, 2008). High consumption of red meat and trans-fat is associated with increased risk of endometriosis, whereas eating fruits, green vegetables, and n-3 long chain fatty acids is associated with decreased risk (Missmer et al., 2010). The risk of developing estrogen-dependent diseases such as breast cancer and endometriosis has been shown to be increased by alcohol consumption (Seitz, Pelucchi, Vecchia, & Bagnardi, 2012; Singletary & Gapstur, 2001). Several studies have investigated the correlation between alcohol consumption and the risk of developing endometriosis with conflicting results (Hemmings et al., 2004; Nagle et al., 2009). A systematic review and meta-analysis on alcohol consumption and endometriosis risk confirmed that an association exists between alcohol intake and risk of endometriosis (Parazzini et al., 2013). However, there is not sufficient evidence to conclude a significant role of environmental toxins and dietary factors in endometriosis aetiology.

Treatment of Endometriosis

As no cure for endometriosis exists, long-term treatment of endometriosis primarily focuses on pain reduction obtained through medical or surgical treatments, or a combination of these two approaches (Giudice, 2010). Individuals often also seek out a range of complementary treatments.

Medical treatments

Medical treatment is typically initiated for pain reduction without surgical confirmation (Giudice, 2010). Pain reduction is obtained through minimising inflammation, interrupting or suppressing cyclic ovarian hormone production, inhibiting the action and synthesis of estrogen, and reducing or eliminating menstruation (Giudice, 2010). To relieve dysmenorrhea, medical professionals commonly prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) on their own or in combination with cyclical, or continuous use of, combined oral contraceptives (Giudice, 2010; Kennedy et al., 2005). Overall, a systematic review showed that GnRH agonists, progestins, oral contraceptives and Danazol were

effective treatment modalities for endometriosis (Jia, Leng, Shi, Sun, & Lang, 2012). These treatment modalities have also been strongly associated with improvement in women's health-related quality of life (HRQoL; (Burry, 1992; Harada et al., 2009; Sesti et al., 2007; Vercellini et al., 2002)).

Surgical treatments

Surgical procedures include conservative and radical surgery. Conservative surgery such as excision or laser ablation of endometrial implants has shown to improve HRQoL in women diagnosed with endometriosis (Abbott et al., 2004; Mabrouk et al., 2011; Roman, 2010; Vercellini et al., 2003). A randomised control trial demonstrated that laparoscopic excision was more effective in reducing pain and improving HRQoL and sexual activity than placebo treatment (Abbott et al., 2004). It is noteworthy, however, that a 30% placebo response rate was observed (41). Radical surgery for endometriosis involves the elimination of all possible endometriosis implants in the pelvic and abdominal cavity and includes hysterectomy and bilateral adnexectomy (De la Hera-Lazaro et al., 2016).

Complementary treatments

Complementary treatments may include homeopathy, dietary supplementation, acupuncture, progressive muscle relaxation (PMR) and Chinese herbal medicine (CHM). A randomised, sham-controlled trial showed that Japanese-style acupuncture was effective for endometriosis-related pain (Wayne et al., 2008). In terms of HRQoL, dietary supplementation after conservative surgery yielded greater improvement compared to surgery alone (Sesti et al., 2007). While a randomised control trial demonstrated the effectiveness of PMR training in improving anxiety, depression and HRQoL in women with endometriosis undergoing hormonal suppression therapy (Zhao et al., 2012). Regular gentle exercise and proper nutrition are generally recommended as alternative therapies (Fromer, 1998); however, data

from large, randomised controlled trials are lacking to confirm the effectiveness of such recommendations.

Impact of Endometriosis on Physical Health

Painful symptoms caused by endometrial implants that proliferate and bleed in conjunction with hormonal cycles are the most common characteristics of endometriosis (Giudice, 2010). Dysmenorrhoea is the most frequently reported symptom of endometriosis (50-90% of cases; (Giudice, 2010). Other pain symptoms include dyspareunia, lower abdominal and back pain, bowel and ovulation pain (Giudice, 2010). Pelvic pain due to endometriosis is typically chronic (lasting six months or longer), and can be dull, throbbing, or sharp in nature. Pain can occur unpredictably and irregularly throughout the menstrual cycle, or it can be continuous, and can in some cases be exacerbated by physical activity (American Society for Reproductive Medicine, 2014). Additional commonly reported symptoms include heavy menstrual flow, bloating, fatigue, infertility (up to 50% of women), and urinary and defecatory dysfunctions (Kennedy et al., 2005). Bladder- and bowel-related symptoms are usually cyclic (American Society for Reproductive Medicine, 2014). Symptoms overlap with several gynaecological conditions (e.g., pelvic inflammatory disease and ovarian cysts) and non-gynaecological conditions (e.g., IBS; (Giudice, 2010)), making diagnosis difficult. Considering the physical symptoms of endometriosis, the associated diagnostic delays, unknown aetiology and incurable nature, it is unsurprising that women diagnosed with endometriosis become more susceptible to poor mental health and reduced quality of life (Sepulcri & do Amaral, 2009).

Impact of Endometriosis on Psychosocial Wellbeing

Endometriosis has significant psychosocial impact on affected women (Culley et al., 2013). A thematic analysis revealed key categories of impact: diagnostic delay and uncertainty, quality of life and everyday activities, intimate relationships, planning for and

having children, education and work, mental health and emotional wellbeing, and medical- and self-management (Culley et al., 2013). It is noteworthy that pain arose as a significant symptom across these categories (Culley et al., 2013). Categories such as diagnostic delay, uncertainty relating to the cause of disease, and management of disease have been explored in earlier sections of this literature review. The following sections will elaborate on mental health, specifically depression and anxiety, intimate relationships, and education and employment and quality of life.

Anxiety and Depression

Overall, studies report higher rates of anxiety, depression and emotional distress in women with endometriosis compared to healthy controls and the general population (Fourquet, Báez, Figueroa, Iriarte, & Flores, 2011; Lorençatto et al., 2006; Petrelluzzi, Garcia, Petta, Grassi-Kassisse, & Spadari-Bratfisch, 2008; Sepulcri & do Amaral, 2009; Siedentopf, Tariverdian, Rucke, Kentenich, & Arck, 2008; Simoens et al., 2012). The prevalence of moderate to severe anxiety and depression in a sample of women with endometriosis was 29% and 14.5%, respectively (Friedl et al., 2015). This is an odds ratio of three compared to prevalence in the general population (general population, anxiety: 8-10%; depression: 4-6% (Friedl et al., 2015)). Additionally, the elevated prevalence of anxiety and depression in women with endometriosis has been found to be comparable to other chronic somatic conditions (Friedl et al., 2015).

Findings regarding the role of pain in poor mental health are inconsistent when comparing women with endometriosis and pain to women with endometriosis without pain (Eriksen et al., 2008; Lorençatto et al., 2006; Sepulcri & do Amaral, 2009). Lorençatto et al. (2006) compared the prevalence of depression in women diagnosed with endometriosis and pelvic pain to women diagnosed with endometriosis without pelvic pain. Depression was found in 86% of women with endometriosis and pelvic pain (mild depression: 34%;

moderate/severe depression: 52%) compared to 36% in women with endometriosis without pelvic pain (mild depression: 24%; moderate/severe depression: 14%) (Lorençatto et al., 2006). This suggests that the experience of pain is a risk factor for depression in women with endometriosis. However, it is unclear whether the assessors were blinded to the presence or absence of pain in women, introducing possible bias to the study's findings. The authors posited that longer periods of pain could potentially lead to higher degrees of pain, and they anticipated higher degrees of pain to be correlated with higher depression scores (Lorençatto et al., 2006). Consistent with the findings of Lorençatto et al. (2006), Sepulcri and do Amaral (2009) found anxiety and depression to be highly prevalent in women with endometriosis and pelvic pain. Out of the 104 women participating, 87.5% reported anxiety (minor anxiety: 24%, major anxiety: 63.5%) and 86.5% showed depressive symptoms (mild depression: 22.1%, moderate: 31.7%, severe: 32.7% (Sepulcri & do Amaral, 2009)). However, no significant correlation was found between pain severity and anxiety and depression, disagreeing with the predictions of Lorençatto et al. (2006).

Contrastingly, Friedl et al. (2015) found the impact of endometriosis to be less than what is reported in other studies. They found moderate to severe anxiety in 29% of women with endometriosis, and depressive symptoms in 14.5% of women (Friedl et al., 2015). Interestingly, Eriksen et al. (2008) were not able to confirm previous findings related to the association between higher anxiety and depression scores in women with endometriosis and pain compared to women with endometriosis without pain. Upon comparing women with endometriosis according to the presence or absence of pain, no significant differences in anxiety and depression scores were found between the two groups (Eriksen et al., 2008). As with several other studies, no correlation between the stage of endometriosis, pain and psychiatric symptoms was reported (Eriksen et al., 2008; Sepulcri & do Amaral, 2009; Tripoli et al., 2011). Friedl et al. (2015) did, however, find women's age to influence their

mental health with advanced age being significantly related to better mental health. A plausible explanation for this is that women who can integrate endometriosis into their daily life feel less stressed and have less frequent affective symptoms (Friedl et al., 2015). When comparing women with chronic pelvic pain due to endometriosis to women with chronic pelvic pain from pathologies other than endometriosis, it becomes clear that the experience of pain is associated with mental health difficulties and emotional stress (Low, Edelmann, & Sutton, 1993; Roth, Punch, & Bachman, 2011; Souza et al., 2011; Waller & Shaw, 1995). Qualitative studies emphasise emotional distress as a key feature for women with endometriosis, including feelings of isolation, hopelessness, guilt, worry, worthlessness, and feeling suicidal (Cox et al., 2003; Moradi, Parker, Sneddon, Lopez, & Ellwood, 2014; Roomaney & Kagee, 2018; Whelan, 2007).

Impact on Intimate Relationships

Incapacitating pain and dyspareunia have been found to adversely impact the quality of women's intimate relationships, with up to 71% of women reporting that endometriosis negatively affects their sexual behaviour (Fourquet et al., 2011). Dyspareunia often leads to women either suffering pain during sexual intercourse, stopping intercourse with their partner after it has been initiated, or being completely unable to engage in penetrative sex (E. Denny & Mann, 2007; Huntington & Gilmour, 2005; Jones, Jenkinson, & Kennedy, 2004b). For 69% of women, dyspareunia has led to pain hours and even days after sexual intercourse (E. Denny & Mann, 2007). The majority of women who experience dyspareunia subsequently avoid or have less frequent sexual intercourse compared to women with asymptomatic endometriosis and healthy controls (E. Denny & Mann, 2007; Jones et al., 2004b; Tripoli et al., 2011). Research demonstrates that women feel that endometriosis (including but not limited to dyspareunia) negatively affects their relationships and has in some instances contributed to relationship breakdown (Cox et al., 2003; Fagervold, Jessen, Hummelshoj, &

Moen, 2009). In terms of fertility, Jones et al. (2004b) reported that infertility, or concerns regarding infertility, led to worry, depression, feelings of inadequacy among women, and contributed to relationship breakdown. In contrast, other studies have found no correlation between infertility and adverse effects on relationships (Fagervold et al., 2009).

Impact on Education and Employment

Findings are inconclusive in regards to the impact of endometriosis on education. Some studies have shown that women's study activity and grades were affected by endometriosis, and some women have left education before completion because of endometriosis (Gilmour, Huntington, & Wilson, 2008). Contrastingly, other studies found that only a minority of women report that they have experienced negative consequences of endometriosis on their education (Fagervold et al., 2009).

The evidence is more consistent when it comes to the impact of endometriosis on employment. Endometriosis has been associated with losses in work productivity with increased disease severity leading to increased loss in productivity (Fourquet et al., 2011; Nnoaham et al., 2011; Tripoli et al., 2011). When symptoms are at their worst, women on average miss 7.41 hours of work per week and miss 19.3 days of work per year (Fourquet et al., 2010). Nnoaham et al. (2011) found a similar trend with a loss of 10.8 hours per week. This was however, primarily attributed to a reduction in effectiveness at work (presenteeism), as opposed to time lost from work (absenteeism) (Nnoaham et al., 2011). Other research suggests that symptoms of endometriosis, especially pelvic pain, affect work productivity with 23% to 66% of women reporting that their ability to carry out work-related activities is limited by their symptoms (Bernuit et al., 2011; Fourquet et al., 2011; Fourquet et al., 2010). Women with endometriosis have been found to report both greater absenteeism and presenteeism compared to women with suggestive symptoms but no endometriosis (symptomatic controls; (Nnoaham et al., 2011)). As a result, full-time employment may be in

jeopardy for some endometriosis-affected women because of increased workplace absence (Gilmour et al., 2008). Some women have expressed that they feel limited to part-time employment because it facilitates the management of their condition much easier than full-time employment (Gilmour et al., 2008).

Quality of Life

Quality of life is a multidimensional construct that incorporates physical, psychological and social aspects of an individual's position in their life (World Health Organisation, 2018). Numerous studies on the quality of life in women diagnosed with endometriosis have yielded conflicting results.

Some research has demonstrated that being diagnosed with endometriosis is enough to significantly affect women's quality of life (Elaine Denny, 2009). Living with endometriosis, whether symptomatic or pain-free, impairs women's quality of life because of the associated uncertainty regarding the course of the disease and the future in general, including concerns about sexuality and infertility (Elaine Denny, 2009). Results from qualitative research indicate that the mere awareness of living with endometriosis is associated with negative feelings, such as being sick, different, and an incomplete woman (Elaine Denny, 2009). Likewise, studies comparing women with endometriosis to symptomatic controls show that women with endometriosis have poorer quality of life than symptomatic controls (Centini et al., 2013; Nnoaham et al., 2011). This implies that the diagnosis of endometriosis is a major contributing factor to reduced quality of life.

Contrastingly, other research implies that endometriosis in itself is not necessarily associated with poorer quality of life and psychological health (Facchin et al., 2015). Instead, the presence of pelvic pain seems to be the determining factor for substandard quality of life and poor mental health. One study examined the impact of endometriosis on quality of life, anxiety and depression by comparing women with asymptomatic endometriosis, women with

endometriosis and pelvic pain, and healthy, pain-free controls (Facchin et al., 2015). Significant between-group effects were found with medium to large effect sizes. Endometriosis with pelvic pain was associated with poorer quality of life and higher anxiety and depression scores compared to the two other conditions. No significant differences were found between women with asymptomatic endometriosis and the control group (Facchin et al., 2015), suggesting that it is not endometriosis per se that gives rise to poorer quality of life and mental health. Instead, the experience of pain seems to play a vital role.

Similarly, in an integrative review of quality of life in women with endometriosis, women with endometriosis were found to have poorer quality of life compared to healthy or asymptomatic controls (Marinho et al., 2018). Endometriosis had an adverse impact on all domains of quality of life, however, this was related more to symptoms than diagnosis as such. Most studies included in the review failed to demonstrate a difference in quality of life between women with endometriosis and women with chronic pelvic pain due to other causes, showing that pain symptoms in particular play a significant role in deteriorating quality of life (Marinho et al., 2018). Additionally, chronic pelvic pain was found to be independently associated with poor quality of life, whereas endometriosis in itself was not (Marinho et al., 2018). Consistent with the review by Marinho et al. (2018), a systematic review on health-related quality of life (HRQoL) in women with endometriosis concluded that HRQoL was impaired in women with endometriosis, and this was primarily due to symptoms like pelvic pain (Jia et al., 2012).

Much like findings with anxiety and depression, quality of life has been found to be positively affected by age (Lövkvist, Boström, Edlund, & Olovsson, 2016). Affected women under 30 years of age reported more disease-related problems than women above 40 years of age, with lower scores in the quality of life domains relating to role-physical, social functioning, role-emotional and mental health (Lövkvist et al., 2016). Perhaps older women

have developed more effective coping mechanisms, despite younger women having been shown to use coping strategies more frequently (Lövkvist et al., 2016). The correlation may be partially explained by more severe symptoms occurring in early-onset disease, by decreasing hormonal levels with aging, by older women having more time to engage in disease management, or a combination of such factors (Marinho et al., 2018).

In regards to infertility and quality of life, it has been found that women with infertility due to endometriosis have lower HRQoL and higher perceived stress levels than women with idiopathic infertility (Siedentopf et al., 2008).

Development of Poorer Psychosocial Wellbeing

One framework that can be used to understand the relationship between endometriosis and the development of poorer psychosocial wellbeing is the biopsychosocial model. The biopsychosocial model provides a holistic understanding of health and illness as it considers the biological (e.g., genetic predisposition, pain symptoms), psychological or behavioural (e.g., depression, lifestyles), and social factors (e.g., relationships, education level) in the varying stages of pathogenesis and health aetiology (see Figure 1) (Engel, 1977; Hatala, 2012). Chronic pelvic pain often affects the psychosocial functioning of endometriosis-affected women (Laganà et al., 2017; Lorençatto et al., 2006), and high levels of depression have been demonstrated to amplify the severity of pain (Laganà et al., 2017). Thus, as explained by the biopsychosocial model, components across the different realms contribute to women's experience of endometriosis. Therefore, if interventions do not address each of the biopsychosocial components of endometriosis, then the vicious circle of chronic pelvic pain and poor psychosocial functioning (psychopathological disease → increased pain → worsening of psychopathological disease) is maintained (Laganà et al., 2017). Hence, adopting a multidisciplinary approach in the management of endometriosis is vital in order to

reduce as much as possible the negative impact of endometriosis on affected women's quality of life and psychosocial wellbeing.

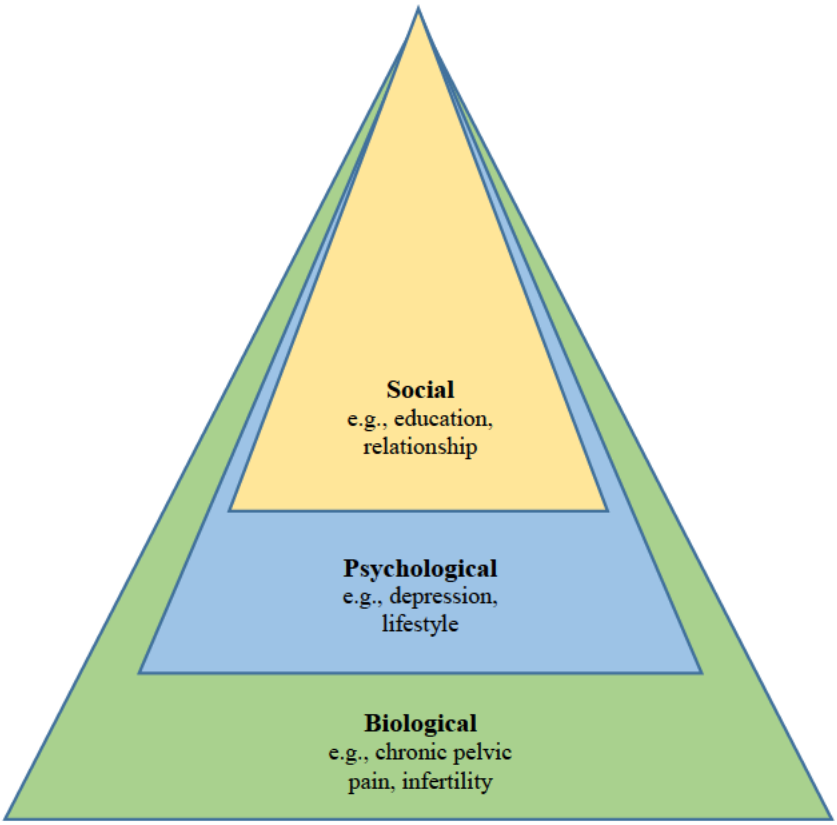

Figure 1. The biopsychosocial model of endometriosis.

Adapted from "Chronic Pelvic Pain in Women" by J.P. Daniels and K.S. Khan, 2010, *BMJ, 341*c:4834.

Future Research

Most studies investigating quality of life in women with endometriosis employ general quality of life instruments that often exclude important issues for women with endometriosis, such as infertility. Future research into quality of life in women with endometriosis ought to utilise endometriosis specific instruments like the Endometriosis Health Profile Questionnaire (EHP-30 (Jones, Kennedy, Barnard, Wong, & Jenkinson, 2001) and EHP-5 (Jones, Jenkinson, & Kennedy, 2004a)). In addition, there is currently minimal research on the psychological impact of experiencing endometriosis and infertility. Thus,

more studies comparing the impact of endometriosis with and without infertility on mental health are warranted to gain a better understanding of the relationship between infertility and endometriosis. Systematic reviews on the impact of endometriosis on mental health and quality of life exist, however, no systematic review has attempted to identify risk factors for poorer mental health and substandard quality of life among women with endometriosis. Given the high prevalence of depression among women with endometriosis and considering the impact of depression on quality of life, future research ought to collate the existing literature on depression in order to identify potential risk factors for depression among women with endometriosis. Such research would contribute to the existing literature by highlighting factors that should be clinically screened and targeted in interventions.

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Psychosocial Risk Factors for Depression Among Women with Endometriosis:

A Systematic Review and Meta-analysis

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Condensation: Endometriosis-affected women who experience anxiety, chronic pelvic pain and dysmenorrhea are more vulnerable to developing depression.

Short title: Psychosocial risk factors for depression in endometriosis.

AJOG at a Glance:

A. Why was this study conducted?
   This systematic review and meta-analysis was conducted because sparse research has examined potential psychosocial risk factors for depression, a condition which is highly prevalent in endometriosis-affected women.

B. What are the key findings?
   Anxiety, chronic pelvic pain, and dysmenorrhea were found to be clinically significant psychosocial risk factors for depression.

C. What does this study add to what is already known?
   This review adds to the existing literature by providing an overview of psychosocial risk factors for depression among endometriosis-affected women. Additionally, the findings of this review emphasise the importance of early screening so that women at greater risk of developing depression can be identified and psychological support offered in a timely manner.

Keywords: anxiety; chronic pelvic pain; depression; dysmenorrhea; endometriosis; mental health; meta-analysis; psychological well-being; risk factor; systematic review.

Abstract

Objective

Existing literature indicates that endometriosis-affected women may suffer poorer psychological wellbeing with depression being highly prevalent. Despite the high prevalence, sparse research has examined potential psychosocial risk factors for depression. Thus, the objective of this systematic review and meta-analysis was to summarise existing research on psychosocial risk factors for depression among women with endometriosis in order to identify areas for clinical assessment and/or intervention.

Data Sources

PubMed, PsycINFO, Web of Science, CINHAL, and Embase were systematically searched from database commencement to September 2018.

Study Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: full-text original article published in the English language, diagnosis of endometriosis clinically or histologically based, depression measured using recognised and validated self-report or clinician-based instruments, psychosocial risk factors for depression were evaluated in at least two studies, and sufficient statistical data to calculate effect sizes was provided. Studies reporting data from multivariate analyses were excluded.

Study Appraisal and Synthesis Methods

Two reviewers assessed the studies. Assessment of risk of bias was carried out using the Joanna Briggs Institute (JBI) critical appraisal tool for analysing cross-sectional studies. Disagreements were resolved through discussion. Effect sizes were calculated and pooled through meta-analysis.

Results

Seven psychosocial risk factors were identified across nine cross-sectional studies (866 women). The psychosocial risk factors were: age, education, marital status, chronic pelvic pain, dysmenorrhea, and dyspareunia. Only anxiety (r = .662), chronic pelvic pain (r = .333), and dysmenorrhea (r = .408) were clinically significant psychosocial risk factors for depression.

Conclusions

These results suggest that endometriosis-affected women who experience anxiety, chronic pelvic pain and dysmenorrhea are more vulnerable to developing depression. Based on these results, early screening for anxiety, chronic pelvic pain and dysmenorrhea are encouraged such that psychological support can be incorporated into endometriosis treatment plans in a timely manner. Further primary research examining psychosocial risk factors for depression among women with endometriosis is recommended in order to draw more firm conclusions about the risk factors identified in the current research and to determine other potential psychosocial and endometriosis-related risk factors for depression in this population.

Introduction

Endometriosis is a gynaecological condition that is characterised by the presence of endometrial tissue outside the uterus, typically found in the abdominal cavity and its surrounding locations (1). The abnormal growth of endometrial tissue results in an estrogen-dependent chronic inflammatory response that is usually associated with chronic pelvic pain, dysmenorrhea, dyspareunia and infertility (2-4). Endometriosis is estimated to affect 2-17% of women, making it one of the most common gynaecological conditions among women of reproductive age (5-7).

Laparoscopic evaluation with subsequent histopathological analyses of biopsies is the gold standard for a definitive diagnosis of endometriosis(8, 9). The aetiology of endometriosis remains controversial; however, several theories have been proposed asserting the influence of immune dysfunction, and genetic and environmental factors in the development of endometriosis (10). The severity of endometriosis can vary from mild to severe with its classification determined by the American Society of Reproductive Medicine (9). Stage I and II represent initial stages of endometriosis, whereas stage III and IV represent advanced stages (11). Pain symptoms of endometriosis have been reported to be independent of the location and stage of disease, meaning that some women with severe endometriosis may be asymptomatic while some women with mild endometriosis may present with severe pain (1, 12, 13).

Besides physical symptoms, women with endometriosis may also experience disturbances in relationships and employment (14-16) as endometriosis has been shown to reduce quality of life and impair the mental health of affected women (4). Depression, the focus of the current review, in particular, has been shown to be a key psychological consequence of endometriosis (4, 17, 18).

For a diagnosis of Major Depressive Disorder (MDD) five or more depressive symptoms must have been present for a minimum of two weeks (19). Depressed mood and/or loss of interest or pleasure must be present along with three to four other symptoms (19). Such symptoms include changes in weight and appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate or make decisions, recurrent thoughts of death or suicidality (19). It is, however, important to note that one can experience depressive symptoms without meeting the full criteria for a diagnosis of MDD. Hence, for this review, an inclusive approach was adopted to include women with endometriosis who experience depressive symptoms.

The prevalence of depression in women with endometriosis has been examined across several studies (12, 20-23). Findings from existing research on the relationship between endometriosis and depression have been inconsistent (12, 18, 24-26). Some research comparing endometriosis patients with healthy controls have not found a significant difference in the prevalence of mood disorders between the two groups (27), suggesting that endometriosis does not significantly impair the mental health of affected women. Contrary, other, more recent, studies have demonstrated that both symptomatic and asymptomatic endometriosis can give rise to poor mental health (1, 12, 25). Interestingly, Eriksen et al. (1) were unable to detect a significant difference in depression levels between women with symptomatic and asymptomatic endometriosis. This suggests that pain symptoms are not the only factors that contribute to the development of depression in women with endometriosis. However, the majority of studies report elevated levels of depression in women with endometriosis who experience pain compared to women with asymptomatic endometriosis (17, 21, 25). For example, Lorençatto et al. (25) observed depression in 86% of women with endometriosis and pelvic pain compared to 36% of women with endometriosis without pelvic

pain. This implies that the experience of pain plays a vital role in the development of depression in women with endometriosis.

Other studies have looked at the relationship between depression and anxiety in women with endometriosis and found the two psychological disorders to be correlated (21, 22, 28, 29). This indicates that in those women with endometriosis who experience anxiety, anxiety may be a non-endometriosis-related risk factor for the onset of depression.

Few studies have explored socio-demographics in relation to depression in women with endometriosis (12, 21, 22). Findings on the influence of age on depression are conflicting with two studies (12, 21) reporting a correlation between advanced age and higher levels of depression, and one study (22) stating that advanced age is related to better mental health. Research on the influence of education level on depression is more consistent, with studies observing an association between low levels of education and high levels of depression (21, 22). This suggests that some socio-demographics are potential psychosocial risk factors for depression in women with endometriosis.

Coping strategies have also been investigated in a small number of studies showing that positive coping strategies are associated with lower levels of depression (1, 20), suggesting coping strategies may be possible psychosocial risk factors for depression in women with endometriosis.

Objective

Despite the existing literature demonstrating that endometriosis is associated with psychosocial implications such as depression, research findings are conflicting. Furthermore, there is sparse research on risk factors for such outcomes. Identifying psychosocial risk factors that increase women's susceptibility to developing depression is crucial for informing preventative strategies, including early detection through assessment, and for treatment with targeted psychological intervention. Thus, this systematic review and meta-analysis aimed to

add to the existing literature by providing an overview of psychosocial risk factors for depression in women with endometriosis. Additionally, suggestions for future research and clinical recommendations will be made based on the findings from this meta-analysis.

Methods

Eligibility Criteria, Information Sources and Search Strategy

Eligibility criteria

Studies were eligible for inclusion in the meta-analysis if they met the following criteria: (i) the diagnosis of endometriosis was clinically and/or histologically based; (ii) depression was assessed using recognised and validated self-report or clinician-based measures; (iii) psychosocial risk factors for depression were evaluated (e.g., age, relationship status, education, pain); (iv) the psychosocial risk factor examined had been included in at least two studies, (v) studies were published in the English language, and lastly; (vi) sufficient statistical data to calculate effect sizes was provided. For this study, a psychosocial risk factor was defined as any variable relating to psychological or social conditions that may significantly contribute to the presence and severity of depressive symptoms.

Opinion articles, editorials, letters to the editor, commentaries, viewpoints, case studies, brief reports, clinical updates, conference abstracts, reviews and qualitative studies were excluded. Studies that investigated endometriosis along with other causes of pelvic pain were excluded if it was not possible to separately extract endometriosis-related data. Equally, studies that grouped multiple psychological disorders were excluded if data on depression could not be extracted separately. Additionally, studies were ineligible if they only reported data from multivariate analyses (e.g., regression, structural equation modelling) as multivariate analyses generate data based on varying combinations of independent and dependent variables, making the data incomparable (30).

Information sources and search strategy

A systematic review of five electronic databases (PubMed, PsycINFO, Web of Science, CINHAL, and Embase) for the period from database commencement up to September 7th 2018, was undertaken to identify articles examining appropriate variants of 'endometriosis' and 'pelvic pain' in combination with 'depression' and 'distress' (See Table A, supplementary material). Search terms were tailored according to the indexing processes of each database to ensure all potentially relevant articles were identified. Additionally, a research librarian was consulted to improve the accuracy and relevance of the search terms. Finally, a manual search of the reference lists of included studies was undertaken to identify any relevant articles that may have been missed in the initial search.

Study Selection

The initial search generated 6798 studies. After the removal of duplicates, 3603 studies remained. Applying the eligibility criteria to the titles and abstracts excluded 3447 studies, leaving 156 studies. The eligibility of these remaining studies was assessed by reviewing the full-texts against the inclusion and exclusion criteria. This narrowed the pool of studies to seven. A manual search of the reference lists of these studies yielded a further two studies appropriate for inclusion. This resulted in nine independent studies being included in the meta-analysis (see Figure 1). A random subset of 360 potentially eligible studies was co-screened by the first author (LST) and a second researcher (MO). Interrater agreement was high (98%, K=.86, $p<.05$) (31) with any discrepancies resolved by consensus discussion.

[INSERT FIGURE 1 HERE]

Data Extraction

Adhering to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) guidelines (32) and the reporting guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE) (33), a data extraction sheet was developed and applied to each study. The data extraction sheet summarised key information such as (i) sample

characteristics (e.g., sample size, age range and mean), (ii) endometriosis characteristics (e.g., method used for diagnosis, type of endometriosis, severity of endometriosis, time since diagnosis), (iii) study characteristics (e.g., study aim, design, comparison groups, recruitment source, measures of depression, measures of psychosocial risk factors), (iv) psychosocial risk factors, (v) effect size estimates (e.g., correlations, *t*-tests, chi-square). Most studies contained sufficient data to undertake some analysis. However, in attempts to enable more comprehensive analysis, twenty-one authors were contacted to obtain additional data on psychosocial risk factors and depression. Four authors (20-22, 34) replied, supplying additional data.

Data extraction was performed by the first author (LST) and verified by a second researcher (MO). Seven potential risk factors were identified: age, education, marital status, anxiety, chronic pelvic pain, dysmenorrhea and dyspareunia.

Assessment of Quality

The Joanna Briggs Institute (JBI) critical appraisal tool for analysing cross-sectional studies (35) was applied to assess the reported methodological quality of studies that met the eligibility criteria. The extent to which each study addressed the possibility of bias was assessed by answering “yes”, “no”, “unclear” or “not applicable” to eight questions concerning study design, conduct and analysis. The assessment was carried out by the first author (LST) and a second critical appraiser (MO) independently with any discrepancies resolved by discussion.

Data Synthesis

For this review, the correlation coefficient *r* was selected as the effect size measure of psychosocial risk factors for depression. The correlation coefficient was chosen because it is easily interpreted with regards to practical importance as it measures the direction of the relationship between a psychosocial risk factor and depression, and the strength of that

relationship (36, 37). Six studies reported other test statistics (χ^2, *t*, sample size with an exact *p*-value for an unreported *r*), which were converted into *r* (30). Effect size data was then recorded and analysed using the statistical software Comprehensive Meta-Analysis Software (CMA, Version 3, Biostat Inc., Englewood, New Jersey, USA). Following the recommendation of Cumming (38), individual effect sizes were pooled using a random-effects model of meta-analysis to calculate the mean effect size of a group of studies. This model is based on the assumption that the variation between observed effect sizes is attributable to differences within individual study designs and subject-level sampling error (30). Although the measures of depression used across studies examining the same psychosocial risk factor varied, the individual effect sizes were still able to be pooled because all of the included measures of depression were standardised and comparable (39).

In line with Cohen's guidelines (40), correlations of .10, .30, and .50 were interpreted as representing small, moderate and large effect sizes, respectively. To determine the statistical significance of the individual effect sizes, *p*-values and 95% confidence intervals (CIs) were calculated. An effect size was considered to be significant if the *p*-value was less than or equal to .05 and the CI did not include zero (38).

To address the possibility that the findings from this meta-analysis were influenced by publication bias, Orwin's fail-safe Ns (N_{fs}) were calculated (41). Publication bias arises when the results of unpublished and published studies are systematically different from each other (41). The N_{fs} represents the number of unpublished or unidentified studies that would need to exist to render the effect size findings of this meta-analysis meaningless (i.e. $r < .10$). A conservative approach was adopted, whereby findings were considered robust when the N_{fs}-value exceeded the number of studies contributing to a pooled effect size estimate (i.e. $N_{fs} > N_{studies}$). Generally, a high N_{fs}-value means it is unlikely that unpublished studies would contradict the findings of the meta-analysis (36).

In addition, heterogeneity was assessed using the I^2 statistic to evaluate the degree of consistency in pooled effect size estimates (42). The I^2-value represents the percentage of observed between-studies variance that can be attributed to an actual difference in effect sizes rather than to chance (43). Values of I^2 around 2%, 50%, and above 50% indicate low, moderate and high heterogeneity, respectively, across individual effect size estimates (44). The I^2-value is not influenced by low statistical power nor by the number of studies included in the meta-analysis (45).

Data Interpretation

A number of criteria were applied to assess the importance of the findings in this review. A psychosocial risk factor was considered clinically and statistically significant if the effect size was (i) moderate to large (i.e. $r \geq .30$), (ii) statistically significant (i.e. $p \leq .05$; 95% CIs $\neq 0$), and (iii) if the associated N_{fs}-value exceeded the number of studies that contributed to the pooled effect size estimate (i.e. $N_{fs} > N_{studies}$). Study heterogeneity was considered in interpreting the results of this meta-analysis.

Results

Study Selection

Study characteristics

Nine cross-sectional studies with publication dates ranging from 2006 to 2018 were included in the meta-analysis (see Table 1). The studies originated from diverse areas of the world: Brazil ($N_{studies}$ = 3), The United States of America ($N_{studies}$ = 2), Italy ($N_{studies}$ = 2), Austria ($N_{studies}$ = 1), and Russia ($N_{studies}$ = 1). Sample sizes ranged from 24 (28) to 214 participants (23).

Almost all studies ($N_{studies}$ = 8) recruited their participants from only one source; one study (12) recruited from two sources. The majority of studies ($N_{studies}$ = 7) relied on hospital Gynaecology and Obstetrics outpatient units for participant recruitment. One study (28)

recruited participants from a patient support organisation (EndoTeens), and another study (29) relied on a regional centre for family planning and reproduction.

Four studies (21-23, 29) included a control group in their study design. Three of the studies compared women with endometriosis to healthy controls, while Lagana et al. (23) compared endometriosis-affected women to women with benign adnexal diseases.

Across the nine studies, four measures of depression were employed. Most studies ($N_{studies}$ = 7) relied solely on self-report measures of depression, with the Beck Depression Inventory (BDI, BDI-II; (46)) being the most commonly used measure ($N_{studies}$ = 6). One study (29) exclusively utilised a clinician rating scale (the Hamilton Depression Rating Scale [HAM-D]; (47)), whereas another study (12) included both a self-report measure (BDI) and a clinician rating scale (HAM-D). For this study, the self-report measure of depression was used in the meta-analysis.

[INSERT TABLE 1 HERE]

Participant characteristics

The total pooled sample comprised 866 women with endometriosis (see Table 2). The age range for endometriosis patients was 18-50 with a mean age of 35.29 (*SD* = 13.04). For those studies that included a control group and reported data on age, the mean age of the controls was 34.48 (*SD* = 10.96). There was no significant difference between the age of the endometriosis patients and the control group (p = .54). Only one study (48) stated ethnicity, with the majority of the women being Non-Hispanic White (7.5%) compared to Black (1.3%). Education levels were reported in six studies (12, 20-22, 28, 48). A slight majority of the women (21.9%) for which this data was reported described their highest educational achievement as high school, closely followed by women describing university as their highest educational achievement (18.7%). A large proportion of the women (46.8%) were in a relationship and employed (15.2%) as opposed to being single (12.2%) and unemployed

(3.2%). The percentages of women with and without children were somewhat comparable at 19.5% and 13.7%, respectively. Initial stage (Stage I and II) endometriosis was more common (13.4%) than advanced stage (Stage II and IV) endometriosis (11.2%). A few women (4%) across two studies (28, 29) reported having a family history of endometriosis, while another study (48) reported a history of depression and/or anxiety for some of the women (4.7%). Over half of the women (55.5%) experienced chronic pelvic pain, more than one-third (37.2%) had dysmenorrhea, and nearly one-fifth (19.2%) experienced dyspareunia as a symptom of endometriosis. Among those with pelvic pain, the average duration of pain was 11.9 years (*SD* = 7.2). Only two studies (20, 21) collected data on fertility, with 85 participants being infertile, representing 9.8% of the pooled patient sample. It was observed across three studies (21, 25, 28) that nearly one-fifth of the women (17.8%) received some form of medical treatment. Smoking history was recorded in three studies (12, 28, 48) with the majority of the women being non-smokers (18.2%) compared to smokers (2.4%). It is important to note that data on the different variables was not consistently reported across all nine studies.

[INSERT TABLE 2 HERE]

Quality Assessment of Included Studies

The reported methodological quality of the studies was examined using the JBI critical appraisal checklist for analytical cross-sectional studies. Results showed that studies fulfilled five to seven criteria, with five studies fulfilling seven criteria, three studies fulfilling six and one study fulfilling five criteria (see Table 3). All studies except for one (28) reported their inclusion criteria. Three studies (22, 23, 28) did not state their exclusion criteria. The majority of the studies ($N_{studies}$ = 7) described their participants and setting in sufficient detail. One study failed to provide information on the setting of their study (21), and another study provided sparse participant information (23). All studies relied on laparoscopy for the

diagnosis of endometriosis except for one study (22) that reported relying on a histologically confirmed diagnosis of endometriosis with no mention of surgery. All studies reported confounding variables, often in the form of some demographical data (e.g., age, relationship status, education, income). However, only a few studies (21-23) stated the strategies utilised to deal with confounding variables. Depression was measured validly and reliably across all studies as only validated and recognised instruments were utilised. In all studies, appropriate statistical tests were used.

It is important to note that the JBI critical appraisal checklist can only assess the reported methodological quality and not the actual methodological quality of studies. Nonetheless, based on the assessment of the reported methodological quality of the included studies, no studies were excluded from the meta-analysis.

[INSERT TABLE 3 HERE]

Synthesis of Results

Seven psychosocial risk factors for depression were identified in this meta-analysis. Of these, only three psychosocial risk factors (anxiety, chronic pelvic pain, and dysmenorrhea) are considered clinically significant according to the criteria adopted in this review (i.e. $r \geq .30$; 95% CIs $\neq 0$; $p \leq .05$; $N_{fs} > N_{studies}$). Effect size estimates varied in their magnitude, as discussed below.

Age

Three studies examined the relationship between age and depression (see Figure 2). Of these, only one study (12) reported a significant but weak relationship between advanced age and depression. The overall effect size estimate was very small and non-significant (r = 0.061, 95% CIs [-.161, .275], $N_{fs} < N_{studies}$, p = .597), suggesting that age was not a psychosocial risk factor for depression. However, this finding should be considered with caution as the N_{fs} statistic was lower than the number of studies included in the analysis,

indicating that the finding may be influenced by publication bias. The between-studies heterogeneity was considerable (I^2 = 69.8%) which would be expected in this clinical population.

[INSERT FIGURE 2 HERE]

Education

The individual correlations from two studies that assessed the relationship between education and depression were not significant (see Figure 3). However, when pooled together, the overall effect size became statistically significant but remained clinically non-significant (r = -.151, 95% CIs [-.295, -.000], $N_{fs} > N_{studies}$, p = .050). Notably, only two studies contributed to the overall pooled effect, meaning the findings should be interpreted with caution. However, N_{fs} was higher than the number of studies included in the analysis, suggesting that this finding is robust. Statistical between-studies homogeneity was found (I^2 = 0%), which could possibly be explained by similarities in study design and population, including the use of identical instruments for measuring depression.

[INSERT FIGURE 3 HERE]

Marital Status

Two studies explored the association between marital status and depression (see Figure 4). Neither of the studies showed a significant correlation. The pooled effect size was also not significant (r = .131, 95% CIs [-.021, .276], $N_{fs} < N_{studies}$, p = .091), indicating that marital status was not a clinically important psychosocial risk factor for depression. However, only two studies were included in the analysis, threatening the strength of this finding, which is also reflected in the small N_{fs} statistic. As the same two studies were pooled for education and marital status, homogeneity (I^2 = 0%) applied for both potential psychosocial risk factors.

[INSERT FIGURE 4 HERE]

Anxiety

Four studies investigated the relationship between anxiety and depression (see Figure 5). Highly significant moderate to large correlations were observed across all studies, resulting in a large and significant pooled effect size (r = 0.662, 95% CIs [.491, .783], $N_{fs} > N_{studies}$, $p < .001$). This implies that experiencing anxiety was a clinically significant psychosocial risk factor for depression. Substantial between-studies heterogeneity was observed (I^2 = 71.8%), which could be partially attributable to the use of varying measures of depression and anxiety across the studies. The associated high N_{fs} indicates that a substantial number of unpublished studies reporting a non-significant relationship between anxiety and depression would need to exist to threaten this finding.

[INSERT FIGURE 5 HERE]

Chronic Pelvic Pain

Six studies assessed the association between chronic pelvic pain and depression. Four out of six studies had significant moderate effect sizes (see Figure 6). The overall pooled effect size was moderate and highly significant (r = 0.333, 95% CIs [.195, .458], $N_{fs} > N_{studies}$, $p < .001$), suggesting that chronic pelvic pain was a clinically significant psychosocial risk factor for depression. The heterogeneity observed between the studies was considerable (I^2 = 69.4%). Considering the high N_{fs} statistic, this finding can be interpreted as robust.

[INSERT FIGURE 6 HERE]

Dysmenorrhea

The individual correlations of two studies that examined the relationship between dysmenorrhea and depression were moderate and highly significant (see Figure 7). The overall pooled effect size was also moderate and highly significant (r = .408, 95% CIs [.236, .555], $N_{fs} > N_{studies}$, $p < .001$). This implies that dysmenorrhea was a clinically significant psychosocial risk factor for depression. The I^2 statistic showed reasonable between-studies

heterogeneity (I^2 = 60.5%), and the N_{fs} statistic suggests that the finding is robust. However, as only two studies contributed to the overall effect size, this result should be interpreted with caution.

[INSERT FIGURE 7 HERE]

Dyspareunia

Two studies explored the association between dyspareunia and depression. Both studies reported a small but significant correlation (see Figure 8). When the studies were pooled, the overall effect size was statistically significant but not clinically significant (r = .183, 95% CIs [.065, .295], $N_{fs} < N_{studies}$, p = .002). Since only two studies were included in the analysis, the finding should be interpreted with caution, which is also reflected in the N_{fs} statistic. The N_{fs} is lower than the number of studies included in the analysis, suggesting that this finding may not be robust and possibly influenced by publication bias.

[INSERT FIGURE 8 HERE]

Comment

Main Findings

This systematic review and meta-analysis investigated potential psychosocial risk factors for depression in women with endometriosis. Nine studies were included with a total of 866 participants. Seven psychosocial risk factors for depression were identified with three of them being clinically significant according to the criteria for this review: anxiety, chronic pelvic pain and dysmenorrhea.

The findings from this meta-analysis suggest that the experiences of chronic pelvic pain and dysmenorrhea are clinically important symptoms of endometriosis that can significantly affect the emotive functioning of affected women by making them more vulnerable to depression. All pain symptoms (i.e., chronic pelvic pain, dysmenorrhea and

dyspareunia) were statistically significant. However, only chronic pelvic pain and dysmenorrhea were clinically significant psychosocial risk factors for depression.

Anxiety demonstrated the strongest relationship with depression with its large clinically significant effect size, suggesting that women with endometriosis who experience anxiety are more likely to experience depression. This makes anxiety a clinically significant psychosocial risk factor for depression.

Strengths and Limitations

To the author's knowledge, this is the first systematic review and meta-analysis that has set out to identify potential psychosocial risk factors for depression in women with endometriosis. Using multiple search terms in combination with thorough inclusion criteria improved the effectiveness and sensitivity of the extensive literature search by increasing the possibility of detecting all relevant articles. Considering that potentially relevant articles could be missed in databases searches, a manual search of reference lists was carried out, and the N_{fs} was calculated to alleviate the 'file drawer problem' to the extent that this statistic allows. The review drew on data from different countries, making the findings cross-culturally applicable and adding to the strengths of the current review.

Some limitations of the present meta-analysis should be taken into account. Only nine studies were eligible for inclusion in this review, with some analyses only including two studies. Analyses that only included two studies should be interpreted with caution as these findings may be more vulnerable to publication bias. Thus, further primary research on the psychosocial risk factors for depression identified in this review is warranted as a larger number of included studies could potentially make the findings more robust and/or suggest other potential psychosocial risk factors for depression (22). Equally, there would be a great benefit in conducting more studies addressing the correlation between endometriosis-related factors and depression in order to accumulate robust evidence that can better inform patient

care. This includes studies investigating the relationship between depression and time since diagnosis, diagnosis delay, endometriosis stage, location of endometriosis, treatment received for endometriosis, fertility status, and demographic information. Furthermore, the study design of all studies included in the current meta-analysis was cross-sectional, making it impossible to make causal inferences. Longitudinal studies are warranted in order to determine the temporal relationship between psychosocial risk factors and depression in women with endometriosis. The small number of studies included in this review highlights the fact that this area is somewhat under-researched, and given the impact on women's wellbeing further investigations are warranted.

Comparison with Existing Literature

The pooled effect size for anxiety concurred with the individual effect sizes of the four studies included in the analysis (21, 22, 28, 29). All effect sizes indicated that anxiety was a statistically and clinically significant psychosocial risk factor for depression. As anxiety and depression are known to co-occur in individuals, with the prevalence of anxiety and depression comorbidity being approximately 60% (49), it is not surprising that anxiety was shown to be a clinically significant psychosocial risk factor for depression.

Similar consistency in results was observed for dysmenorrhea with both the overall effect size and the individual effect sizes of the included studies (20, 21) being statistically and clinically significant. This indicates that experiencing dysmenorrhea renders affected women more vulnerable to depression.

The overall pooled result of the chronic pelvic pain analysis is consistent with some of the existing literature (20, 21, 25), indicating that chronic pelvic pain is a statistically and clinically significant psychosocial risk factor for depression. However, this result contrasts the findings of Carey et al. (48) and González-Echevarría et al. (28) as their results did not reach statistical significance. Nonetheless, research has demonstrated that chronic pelvic pain

has significant adverse effects on women's mental health and quality of life (1, 13, 26, 50-53).

Being statistically significant but not clinically significant, the pooled result for dyspareunia was consistent with the results of the individual studies included in the analysis (21, 23). Research has shown that women who experience dyspareunia engage in less sexual behaviour (13, 54). This could explain why dyspareunia, unlike the other endometriosis-related pain symptoms, was not a clinically significant psychosocial risk factor for depression. Women affected by dyspareunia can avoid experiencing this type of pain, contrasting the experience of chronic pelvic pain and dysmenorrhea, which cannot be avoided or controlled in similar ways to dyspareunia.

Neither the individual results of the two included studies exploring the relationship between depression and marital status (21, 22) nor the pooled result were statistically or clinically significant. This suggests that relationship status does not influence affected women's likelihood of developing depression.

The research relating to age and depression is conflicting. Unlike the overall finding of this meta-analysis, Sepulcri and do Amaral (12) reported a statistically and near clinically significant relationship between advanced age and depression. However, similar to the overall result of this meta-analysis, Facchin et al. (21) did not find a clinically or statistically significant relationship between advanced age and depression. Contrasting the direction of the relationship between age and depression in both of those studies (12, 21) and this meta-analysis, Friedl et al. (22) observed a small albeit non-significant effect of younger age on depression. Plausible explanations for a relationship between younger age and depression could relate to decreasing hormonal levels with ageing and potentially more time to engage effectively in the management of the condition (55). Nevertheless, the pooled data in this meta-analysis suggest that age is not a psychosocial risk factor for depression.

The pooled result on education just reached statistical significance. However, the small effect size concurred with previous research (21, 22) showing that educational level is not a clinically significant psychosocial risk factor for depression.

Conclusion and Implications

The findings from this systematic review and meta-analysis have implications for the research and management of endometriosis. In the process of writing this review, potential psychosocial risk factors other than the ones included in the review were identified, e.g., fatigue, coping strategies, and sexual functioning. The few studies that investigated coping strategies and depression employed incomparable measures of coping and did not report sufficient statistics to calculate an effect size. Hence, pooling of effect size data was not possible for coping strategies in this review. Equally, studies examining fatigue and depression, and sexual functioning and depression, only reported multivariate analyses and thus, could not be included in this meta-analysis. Primary research on the relationship between depression and each of the following, coping strategies, fatigue, and sexual functioning is warranted such that more robust conclusions regarding these relationships can be made.

Clinical implications resulting from the current review include the importance of early screening to accurately identify those at greater risk of developing depression. Screening and assessment for depression should not only take place upon diagnosis of endometriosis but throughout the continuum of endometriosis management, as some psychosocial risk factors (e.g., anxiety) may not be present at diagnosis but may occur later in the course of the condition. Through early screening and identification of the presence of anxiety, chronic pelvic pain and dysmenorrhea, the risk of depression and its severity may be reduced for women with endometriosis. Early identification would allow psychological support to be incorporated into an individual woman’s treatment plan. The aim of such a multidisciplinary

approach in the management of women with endometriosis should be to reduce the adverse impact of endometriosis on the women's psychosocial wellbeing and consequently, their quality of life.

In summary, endometriosis is a very complex condition that makes affected women more vulnerable to compromised psychosocial wellbeing. Anxiety, chronic pelvic pain, and dysmenorrhea were found to be clinically significant psychosocial risk factors for depression. These psychosocial risk factors should be considered in the management of endometriosis to improve women's psychosocial wellbeing and quality of life. Further primary research investigating the seven identified potential risk factors and other potential psychosocial risk factors such as fatigue, coping strategies and sexual functioning along with other endometriosis-related factors (e.g., diagnostic delay, location, treatment received, fertility status) is warranted in order to draw more firm conclusions regarding potential risk factors for depression in women with endometriosis.

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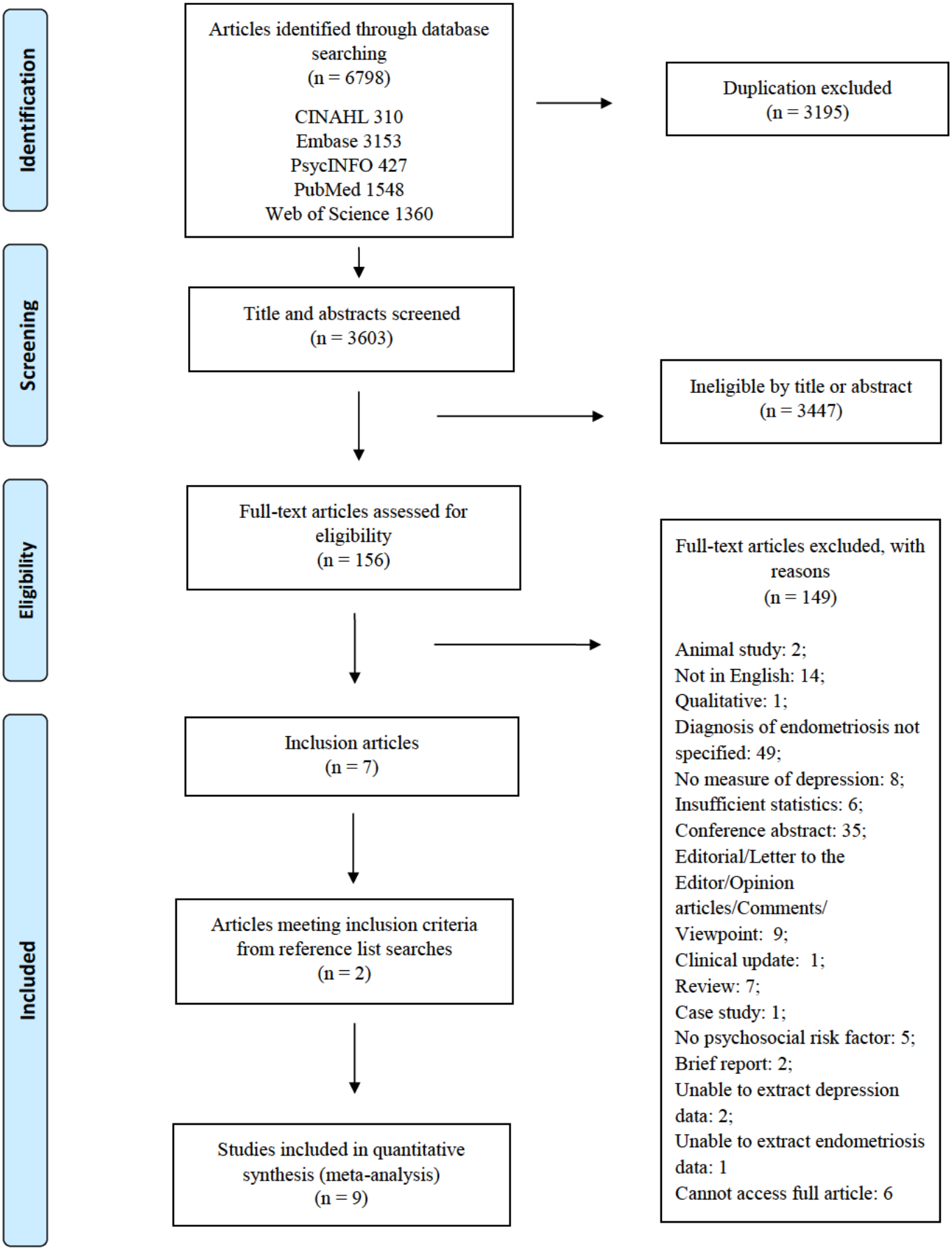

Figure 1. PRISMA Flow Chart of the study selection process. Adapted from "*P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statemen" by Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009), PLoS Med 6(6): e1000097.

Table 1

Characteristics of Included Studies

Lead Author	Country	Sample size (Endometriosis patients)	Recruitment source	Depression Measure	Risk Factors Measured
Carey (2014)	United States	79 (79)	Hospital Outpatient Unit for Endometriosis	BDI	Chronic Pelvic Pain
Donatti (2017)	Brazil	171 (171)	Hospital Outpatient Unit for Endometriosis	BDI	Chronic Pelvic Pain; Dysmenorrhea; Coping Style; Stress
Facchin (2015)	Italy	171 (110)	Hospital Outpatient Unit for Endometriosis	HADS-D	Chronic Pelvic Pain; Dysmenorrhea; Dyspareunia; Anxiety; Age
Friedl (2015)	Austria	123 (62)	Hospital Outpatient Unit for Endometriosis	HADS-D	Anxiety
González-Echevarría (2018)	United States	24 (24)	Patient Support Organisation "EndoTeens"	BDI-II	Anxiety; Chronic Pelvic Pain
Lagana (2015)	Italy	214 (166)	Hospital Outpatient Unit for Endometriosis	The Zung Self-Rating Depression Scale	Chronic Pelvic Pain; Dyspareunia
Lorencatto (2006)	Brazil	100 (100)	Hospital Outpatient Unit for Endometriosis	BDI	Chronic Pelvic Pain
Nasyrova (2011)	Russia	80 (50)	Regional Centre for Family Planning and Reproduction	HAM-D	Anxiety
Sepulcri (2009)	Brazil	104 (104)	Two Hospital Outpatient Units for Endometriosis	BDI; HAM-D	Age

Note. Measure Abbreviations: BDI = Beck Depression Inventory; BDI-II = Beck Depression Inventory-II; HADS-D = Hospital Anxiety and Depression Scale-Depression; HAM-D = Hamilton Depression Rating Scale.

Table 2

*Participant Sociodemographic and Endometriosis Characteristics ($N_{studies}$ = 9)**

Variable	Endometriosis Patients				Control				Statistical Analysis				
									95% CI				
	$N_{Studies}$ [a]	$N_{Participants}$ (%)[a,b]	*M (SD)*	Range	$N_{Studies}$ [a]	$N_{Participants}$	*M (SD)*	Range	Lower	Upper	t	df	*p*
Sample Size	9	866 (100)	96.2 (49.4)	24-171	3**	170	56.7 (6.13)	48-61					
Age (y)	7***	732	35.29 (13.04)	18-50	2	109	34.48 (10.96)	Not given	-3.39	1.77	-0.62	839	0.54
Ethnicity													
Non-Hispanic White	1	65 (7.5)											
Black	1	11 (1.3)											
Level of Education													
High school	5	190 (21.9)											
University	4	162 (18.7)											
Technical degree	1	7 (0.8)											
Employment													
Yes	2	132 (15.2)											
No	2	28 (3.2)											
Marital Status													
Partnered/Married	7	405 (46.8)											
Single/Widowed	4	106 (12.2)											
Parous													
Children	3	169 (19.5)											
No children	3	119 (13.7)											
Endometriosis Stage													
I-II	3	116 (13.4)											
III-IV	3	97 (11.2)											
Family History of Endometriosis	2	35 (4.0)											
Pain													
Chronic Pelvic Pain	6	481 (55.5)											
Dysmenorrhea	4	322 (37.2)											
Dyspareunia	3	166 (19.2)											
Duration of Pelvic Pain (yrs)	1	79 (9.1)	11.9(7.2)										
Infertility	2	85 (9.8)											
Receiving Medical Treatment	3	149 (17.2)											
History of Depression and/or Anxiety	1	41 (4.7)											
Smoker													
Yes	2	21 (2.4)											
No	3	158 (18.2)											

Note. * not all studies provided this data for their endometriosis and control groups. $N_{Studies}$ = the number of studies providing data; $N_{Participants}$ = the number of participants with endometriosis for which data was provided; [a] Number varies within columns because not all studies reported this information; [b] Percentage (%) of participants is in relation to the total sample of

endometriosis patients; M = Mean; SD = standard deviation; 95% CI = 95% confidence interval with lower and upper limits; **Four studies used control groups but one study did not report the number of health controls included in their study, therefore only data from three studies are reported.***All studies reported age, however, in one study, it was impossible to separate the mean age and standard deviation for patients and controls, and another study only reported the percentage of patients in the age ranges 13-19 years and 20-25 years.

Table 3

Assessment of Quality for Included Studies using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (Moola et al., 2017)

Studies	1. Were the criteria for inclusion in the sample clearly defined?	2. Were the study subjects and the setting described in detail?	3. Was the exposure measured in a valid and reliable way?	4. Were objective, standard criteria used for measurement of the condition?	5. Were confounding factors identified?	6. Were strategies to deal with confounding factors stated?	7. Were the outcomes measured in a valid and reliable way?	8. Was appropriate statistical analysis used?	Overall Appraisal
Carey et al. (2014)	●	●	●	●	●	○	●	●	Include
Donatti et al. (2017)	●	●	●	●	●	○	●	●	Include
Facchin et al. (2015)	●	◗	●	●	●	●	●	●	Include
Friedl et al. (2015)	◗	●	◗	◗	●	●	●	●	Include
González-Echevarría et al. (2018)	○	●	●	●	●	○	●	●	Include
Lagana et al. (2015)	◗	◗	●	●	●	●	●	●	Include
Lorencatto et al. (2006)	●	●	●	◗	●	◗	●	●	Include
Nasyrova et al. (2011)	●	●	●	●	●	○	●	●	Include
Sepulcri & Amaral (2009)	●	●	●	●	●	○	●	●	Include

Note. ●= yes, ○= no, ◓ = unclear

Lead Author	Depression Measure	$N_{Studies}$	$N_{Particioants}$	*R*	95 Lower
Facchin (2015)	HADS-D			.067	-.122
Friedl (2015)	HADS-D			-.171	-.404
Sepulcri (2009)	BDI, HAM-D			0.243	.053
Overall		**3**	**276**	**.060**	**-.161**

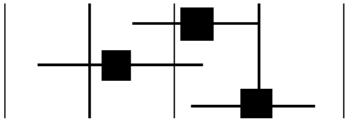

Figure 2. Depression by age. A positive and significant effect would indicate that advanc

Lead Author	Depression Measure	$N_{Studies}$	$N_{Particioants}$	*R*	95 Lower
Facchin (2015)	HADS-D			-.128	-.308
Friedl (2015)	HADS-D			-.192	-.422
Overall		**2**	**172**	**-.151**	**-.295**

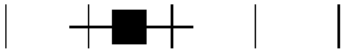

Figure 3. Depression by education. A negative and significant effect indicates that lower l

Lead Author	Depression Measure	$N_{Studies}$	$N_{Particioants}$	*R*	95 Lower
Facchin (2015)	HADS-D			.128	-.061
Friedl (2015)	HADS-D			.135	-.119
Overall		**2**	**172**	**.131**	**-.021**

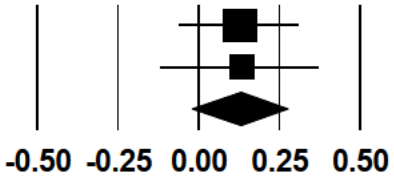

Figure 4. Depression by marital status. A positive and significant effect would indicate that l

etriosis.

Lead Author	Depression Measure	$N_{Studies}$	$N_{Particioants}$	*r*	95% Lower
Facchin (2015)	HADS-D			.625	.496
Friedl (2015)	HADS-D			.751	.617
González-Echevarría (2018)	BDI-II			.812	.608
Nasyrova (2011)	HAM-D			.410	.149
Overall		**4**	**246**	**.662**	**.491**

Figure 5. Depression by anxiety. A positive and significant effect indicates that experienci

Lead Author	Depression Measure	$N_{Studies}$	$N_{Particioants}$	*r*	95% Lower
Carey (2014)	BDI			.038	-.185
Donatti (2017)	BDI			.330	.189
Facchin (2015)	HADS-D			.493	.337
González-Echevarría (2018)	BDI-II			.322	-.094
Lagana (2015)	Zung SRDS			.250	.102
Lorencatto (2006)	BDI			.495	.330
Overall		**6**	**650**	**.333**	**.195**

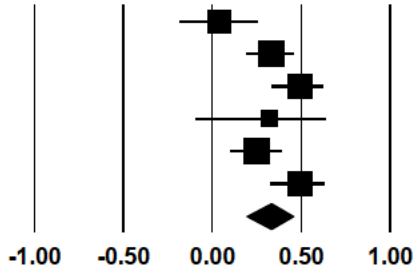

Figure 6. Depression by chronic pelvic pain. A positive and significant effect indicates tha
endometriosis.

Lead Author	Depression Measure	$N_{Studies}$	$N_{Particioants}$	*r*	9 Lowe
Donatti (2017)	BDI			.330	.190
Facchin (2015)	HADS-D			.493	.337
Overall		**2**	**281**	**.408**	**.236**

Figure 7. Depression by dysmenorrhea. A positive and significant effect indicates that ex iosis.

Lead Author	Depression Measure	$N_{Studies}$	$N_{Particioants}$	*R*	9 Lower
Facchin (2015)	HADS-D			.217	.031
Lagana (2015)	Zung SRDS			.160	.008
Overall		**2**	**276**	**.183**	**.065**

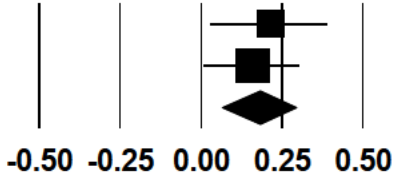

Figure 8. Depression by dyspareunia. A positive and significant effect indicates that experienc s.

Supplementary Material

Table A

Logic Grids for Electronic Database Searches

PubMed – 1548

Endometriosis 51469	Depression 534566
“endometriosis”[mh] OR “pelvic pain”[mh] OR “menstruation disturbances”[mh:noexp] OR “menorrhagia” [mh] OR “dyspareunia” [mh] OR endometriosis[tiab] OR pelvic pain[tiab] OR menstruation disturbance*[tiab] OR painful period*[tiab] OR heavy period*[tiab] OR painful intercourse[tiab] OR dyspareunia[tiab] OR dysmenorrhea[tiab] OR menstrual disorder*[tiab] OR menstruation disorder*[tiab]	“depression”[mh] OR “depressive disorder”[mh] OR depress*[tiab] OR distress[tiab]

PsycINFO - 427

Endometriosis 1877	Depression 324660
(menstrual disorders).sh OR dyspareunia.sh OR dysmenorrhea.sh OR endometriosis.ti,ab OR pelvic pain.ti,ab OR painful period*.ti,ab OR heavy period*.ti,ab OR painful intercourse.ti,ab OR dyspareunia.ti,ab OR dysmenorrhea.ti,ab OR menstrual disorder*.ti,ab OR menstruation disorder*.ti,ab	(depression emotion).sh OR exp major depression OR depress*.ti,ab OR distress.ti,ab

Web of Science - 1360

Endometriosis 37399	Depression 667156
TS=(endometriosis OR “pelvic pain” OR “painful period*” OR “heavy period*” OR “painful intercourse” OR dyspareunia OR dysmenorrhea OR “menstrual disorder*” OR "menstruation disturbances" OR menorrhagia OR "menstruation disorder*")	TS=(depress* OR distress)

CINAHL – 310

Endometriosis 6417	Depression 108907
MH endometriosis OR MH “pelvic pain” OR MH “menstruation disorders” OR MH dysmenorrhea OR MH dyspareunia OR MH menorrhagia OR TI endometriosis OR AB endometriosis OR TI “pelvic pain” OR AB “pelvic pain” OR TI “menstruation disturbance*” OR AB “menstruation disturbance*” OR TI “painful period*” OR AB “painful period*” OR TI “heavy period*” OR AB “heavy period*” OR TI “painful intercourse” OR AB “painful intercourse” OR TI dyspareunia OR AB dyspareunia OR TI dysmenorrhea OR AB dysmenorrhea OR TI “menstrual disorder*” OR AB “menstrual disorder*” OR TI “menstruation disorder*” OR AB “menstruation disorder*”	MH depression OR TI depress* OR AB depress* OR TI distress OR AB distress

Embase - 3127

Endometriosis 64707	Depression 762235
Endometriosis/de OR “pelvic pain/de” OR “menstruation disorder/de” OR dysmenorrhea/de OR menorrhea/de OR dyspareunia/de OR endometriosis:ti,ab OR “pelvic pain”:ti,ab OR “menstruation disturbance*”:ti,ab OR “painful period*”:ti,ab OR “heavy period*”:ti,ab OR “painful intercourse”:ti,ab OR dyspareunia:ti,ab OR dysmenorrhea:ti,ab OR “menstrual disorder*”:ti,ab OR “menstruation disorder*”:ti,ab	Depression/de OR depress*:ti,ab OR distress:ti,ab

Author Information

Article Types

- Every submission must include a title page with a disclosure statement and a signed statement of authorship form. This requirement applies to ALL article types listed in the following section; including letters, replies, etc.
- The editors encourage the supplementary use of multimedia components such as PowerPoint, additional images, or video clips. Color figures and images are free.

Original Research

Systematic review and meta-analysis studies: please refer to Systematic Reviews

Translational Research: please refer to Translational Research

Systematic Reviews
Each article in this category provides a comprehensive and exhaustive systematic review of the literature related to the topic, collating all relevant evidence meeting pre-specified eligibility criteria. Systematic reviews may not be combined with other manuscript types.

Systematic reviews must include a clearly stated set of objectives with reproducible methodology, a systematic search, eligibility criteria for selecting studies, assessment of study quality (risk of bias), an assessment of the validity of the findings and systematic synthesis of these findings. Metaanalysis, the use of statistical techniques to combine and summarize results across studies, may or may not be contained within a systematic review.

Authors must adhere to the PRISMA and MOOSE guidelines (for guidance see Editorial Policies).

Systematic Reviews are limited to 5000 words of main text (not counting the title page, abstract, condensation, acknowledgments, references, tables, legends, and figures). Include a structured abstract containing no more than 350 words and as many alphabetized key words or short phrases as needed for indexing.

Title: The title should identify the report as systematic review or metaanalysis.

The type(s) of non-human animals or other species used in an investigation must be named in the Title, Abstract, and Materials and Methods sections of the manuscript.

On the next page supply:

Condensation, Short Title, AJOG at a Glance, and Keywords

- Condensation - a 1-sentence condensation of the paper, consisting of no more than 25 words, stating its essential point(s); this sentence, which is subject to copy editing in conformance with Journal style, will appear in the Table of Contents.
- Short Title: a short version of the article title, for the identification line inserted at the bottom of each published table and figure.
- AJOG at a Glance: This section is limited to no more than 130 words, 1-3 short sentences or phrases in bullet form, briefly describing your study, its significance, and its contribution to the literature. *Include the questions followed by your responses,* and listed in bullet form with A., B., and C., headings (not in paragraph form). All responses are subject to minor editorial alterations and/or shortened without the authors' approval, and published on the Journal website.

A. Why was this study conducted?

B. What are the key findings?

C. What does this study add to what is already known?

- Keywords - Keywords are a pertinent component in making articles more visible and accessible to potential readers and assist in the dissemination of your research. Provide as many alphabetized key words or short phrases as needing for indexing purposes. Approximately 10 terms are recommended, but do not duplicate terms or phrases utilized in the manuscript title as they are automatically included.

On the next page supply:

Abstract: Include a structured abstract containing no more than 350 words in accordance with PRISMA guidelines, and with the following headings:

- Objective
- Data sources (including years searched)
- Study eligibility criteria (study design, populations, and interventions [if applicable])
- Study appraisal and synthesis methods
- Results
- Conclusions

Main text: Headings and subheadings in the main text should include the following; note that subheadings may be modified to best represent the specific report.

- Introduction (rationale, explain impetus for Review)
- Objective(s)
- Methods

  Eligibility criteria, information sources, search strategy
  Study selection
  Data extraction
  Assessment of risk of bias
  Data synthesis

- Results

  Study selection
  Study characteristics
  Risk of bias of included studies
  Synthesis of results

- Comment

  Main findings
  Strengths and limitations
  Comparison with existing literature
  Conclusions and Implications

Basic Format

Requirements for manuscripts submitted to the Journal generally conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals from the International Committee of Medical Journal Editors (http://www.icmje.org).

Manuscripts must be submitted in American English, double spaced, with a font size no smaller than 12. Number pages consecutively in the upper right corner in the following order: title page, condensation and short version of title, abstract, main text, acknowledgments, references, tables, and figure legends.

IMPORTANT: Figures are to be uploaded individually and in separate files (one figure per file). **DO NOT embed the figure into the manuscript text file**, as this compromises the image quality, creating an unpublishable image (see artwork).

References

Follow the format in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals from the International Committee of Medical Journal Editors. http://www.icmje.org Standard journal title abbreviations are available in the List of Serials Indexed for Online Users from the National Library of Medicine.
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Numbering and order

All references are to be numbered sequentially as they fall in the text. For references that are not cited in the main text but only within table(s) or figure(s), begin such numbering *after* the numbers in the main reference list.

Insert citations in Arabic numerals as superscripts, not in parentheses. If the reference follows a comma or falls at the end of a sentence, the superscript should follow the comma or the period.

Do not include the first author of the cited reference in the text, in parentheses or otherwise, except as part of the text itself (Smith et al found…. or In a study by Smith et al, ...).

If any reference is repeated or out of order, the author is responsible for renumbering references as needed prior to submission or resubmission. If any reference(s) are added or deleted during editing, the author is responsible for renumbering all subsequent references, both in citations within the text (and tables and figures) and, correspondingly, in the reference list. For any citations used in tables or figure legends, renumbering should similarly be done there.

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In general references follow AMA style.

For up to 6 authors, list all; for 7 or more authors, list the first 3 + et al.

•**Journal article**

Nageotte MP, Vander Wal B. Achievement of the 30-minute standard in obstetrics—can it be done? Am J Obstet Gynecol 2012;206:104-7.

•Book chapter or section
Kim M. Amenorrhea: primary and secondary. In: Zuspan FP, Quilligan ED, eds. *Handbook of obstetrics, gynecology, and primary care.* St Louis, MO: Mosby; 1998:3-10.

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Abstracts of scientific meetings can be cited; however; once the complete work is published, the article citation is preferred.

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Journal names should be abbreviated according to the List of Title Word Abbreviations: http://www.issn.org/services/online-services/access-to-the-ltwa/.

Provisional patent applications
Provisional patent applications may not be cited as a reference.

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Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is encouraged.

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Please ensure that the words ‘this issue’ are added to any references in the list (and add any citations in the text) to other articles in the same Special Issue.

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Websites may or may not be appropriate sources for citation; e.g., websites that serve as repositories of genetic information maintained by NIH, NCI, and the National Library of Medicine are acceptable.

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Tables

Submit tables in the manuscript file at the conclusion of the reference list and before the figure legends. Create all tables as double-spaced text in Microsoft Word. Any table submitted as a *.jpg or *.tif file will be returned for replacement.

Identify each table with a *brief* title (as few words as possible; reserve abbreviations for the key) and with an Arabic number (Table 1, Table, 2, etc.) in the order in which it is cited in the text. Each column, including the first, must have a heading. Put all explanatory matter in footnotes, including the spelling out of any nonstandard abbreviations used in the table.

For footnote symbols within tables, follow the style and order noted on pages 90-95 of the AMA style guide, 10th edition. For placement, start in the upper left corner and work across, left to right, and down, line by line.

If a table, in whole or in part, was derived from copyrighted material, a footnote at the bottom of the table must credit the original source, cited fully. Any copyrighted material must be accompanied by **a letter or completed permission form** at the time of manuscript submission.

Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

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