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LETTER TO THE EDITOR

# Endometriosis and depression: only a psychological effect or even a causal occurrence?

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Endometriosis represents one of the most common gynecologic conditions characterized by the formation of abnormal endometrial-like-tissue outside the uterus [1]. Accumulated evidence has shown that endometriosis exerts adverse effects on mental health causing a wide range of psychological symptoms [1]. Depression has been reported as the predominant and debilitating mental health condition among women with endometriosis [1]. Gonadotropin-releasing hormone agonists (GnRH) agonists utilized in the treatment of endometriosis have been associated with depressive symptoms suggesting the decline in estrogen levels as a reason [2]. Moreover, the chronic pain that affects the well-being of endometriotic women has been suggested to make them angry, short-tempered and even depressed [1]. On this regard, the presence of endometriosis has been related to a specific phenotype involving menstrual pain severity and duration as well as gastrointestinal symptoms and widespread pain [3]. It has been specified that patients affected by endometriosis suffer from more menstrual pain, cramps, bloating, and widespread pain when compared with women reporting menstrual pain without endometriosis [3]. The exact pathological basis of endometriosis remains as yet undefined [1]. Impaired immune functioning has been found among the underlying mechanisms of this condition [1]. Endometriosis has been described as a chronic inflammatory disease connected with a dysregulated immune response to endometrial cells facilitating the implantation and proliferation of ectopic endometrial tissues [4, 5]. Myeloid-derived suppressor cells (MDSCs) have been observed to play an important role in the progression of endometriosis [4, 5]. MDSCs constitute a heterogeneous population of immature myeloid cells with immunosuppressive and angiogenic properties [4]. The generation of MDSCs following endometriosis has been detected in both humans and in the mouse model [2]. MDSCs have been shown to be considerably increased in peripheral blood of patients with endometriosis and in the peritoneal cavity of a mouse model of surgically induced endometriosis [4]. Concordantly, reduction of MDSCs has been identified to dramatically inhibit the development of endometrial lesions in mice [4]. Regulatory T cells (Tregs) dysfunction has been verified to worsen endometriosis [5]. Tregs appear to play a critical role in T cell-mediated immune response and development of immune disorders [5]. It has been documented that there is a reduction of true suppressive activated Tregs in women with endometriosis and progression of endometriosis [5]. It has been revealed that in women with endometriosis the proportion of activated Tregs in the endometrioma and endometrium is significantly lower in comparison to that in women without endometriosis [5]. Low expression of suppressive Tregs has been associated with a reduced ability of newly recruited leukocytes to initiate effective immune responses against viable endometrial fragments, permitting their survival [5]. It has been documented that Tregs deficiency enhances local inflammation and angiogenesis and simultaneously promote the attachment and growth of endometrial implants [5].

Depression is a very common illness of the Central Nervous System (CNS) [6, 7]. It has been shown that major depression is closely linked to a dysregulation of immune system [6]. There is increasing evidence to suggest that neuroinflammation stimulates abnormal cellular immunity and increases predisposition to psychiatric disorders [6]. Inflammation has been implicated in depression pathophysiology and its potential in the treatment for depression [6, 7]. MDSCs have been evidenced to be a major suppressor of immune responses [6]. It has been found that MDSCs participate actively in the impairment of T cell responses in

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patients with major depression [6]. MDSCs from patients with major depression have been demonstrated to strongly suppress T cell function [6]. It has been verified that the proportion and the absolute number of MDSCs are increased in the peripheral blood of major depression patients, in comparison to healthy controls [6, 7]. A decrease in circulating Tregs has been connected with the pathogenesis of major depressive disorder [7]. Both human and animal studies have confirmed that there is an interplay between an increased risk of major depression and a reduced number of Tregs in a contest of inflammation [7]. Adolescents at high risk for mood diseases have been reported to exhibit a decreased number of Tregs that is negatively connected with their inflammatory state [8]. Tregs insufficiency found in many disorders with an inflammatory component reinforces the link between inflammation and depression explaining the high rate of major depressive disorders in these categories of patients [7].

Taken together, we hypothesize that endometriosis and depression may coexist as interrelated phenomena within the same patients not only as a psychological effect but even as a causal occurrence. We advise bidirectional increases in risk of comorbidity for women with both endometriosis and depression. We think that these two conditions may arise from a similar pathological immune network involving MDSCs and Tregs highlighting that immune dysregulation may represent a causal relationship between these two conditions. In detail, we speculate that women with endometriosis may experience depression in response to increased levels of MDSCs and decreased expression of Tregs, features common to both diseases. "We believe that further investigation is required to elucidate the common pathophysiology for both endometriosis and depression to gain an understanding of the relationship of the pathways to implement a common type of therapy. If that is the case, we suggest that women with endometriosis should be counselled about the risk of major depression to promptly receive the right support.

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## Declarations

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