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## Endometriosis and type 1 allergies/immediate type hypersensitivity: a systematic review

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### ABSTRACT

Endometriosis is a chronic and debilitating disorder affecting up to 5–10% of women in reproductive age. Investigators have described deficiency in cellular immunity in women suffering from endometriosis, and in the recent years endometriosis has been linked to other diseases, allergic disease being one of them. The objective of this paper is to systematically review the existing literature on the possible association between endometriosis and allergic disease. This review is based on the recommendations by the preferred reporting of systematic reviews and meta-analysis (PRISMA) statement.

PubMed and Embase were searched for studies on women diagnosed with endometriosis and with manifestations of allergic disease who were compared to a reference group. Out of 316 articles screened, 6 were reviewed and 5 ultimately met the inclusion criteria. Four out of the five studies reported a positive correlation between endometriosis and allergic manifestations, including hay fever, sinus allergic rhinitis, and food intolerance/sensitivities (food allergy). Investigators reported an odds ratio (OR) as high as 4.28 (95% CI: 2.93–6.27) for a positive history of allergy among women suffering from endometriosis. Equivocal results were found on asthma prevalence in women with endometriosis. Due to the heterogeneity of the included studies, no meta-analyses could be performed.

The available literature clearly indicates that women with endometriosis are at an increased risk of allergic disorders compared to controls, but due to the lack of a concise definition of allergic disease and therefore diagnostic criteria, further studies are needed in order to draw firm conclusions on the association between endometriosis and allergic disease.

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### Introduction

Endometriosis is defined by the presence of functional endometrial tissue outside the uterine cavity, usually located in the pelvis, but can also be present in other regions [1].

The prevalence of endometriosis is estimated to be 5–10% of women of reproductive age and as high as 30–50% in symptomatic women. Most women with endometriosis typically suffer from different pelvic pain symptoms, including dysmenorrhea, dyspareunia and pain during ovulation [1,2]. Furthermore, the prevalence of infertility among women suffering from endometriosis is as high as 30–50% [3]. Existing treatment for pain and infertility includes hormone therapy and surgical removal of implants/lesions [4]. Despite extensive treatment many women still suffer from

frequent symptoms, in particular chronic pelvic pain. Endometriosis has an impact on education, work and social well being resulting in a lower quality of life for women affected by this enigmatic disease [5]. Additionally, the economic burden of endometriosis is substantial [6].

Multiple hypotheses have been proposed regarding the aetiology of endometriosis, with one of the most accepted being Sampson's theory of retrograde menstruation [7]. However, since retrograde menstruation is a common phenomenon in reproductive women, other mechanisms must be involved in the formation of endometriotic implants. Despite numerous research efforts the pathogenesis of endometriosis remains unknown.

Deficiency in cellular immunity in women suffering from endometriosis was first described in 1981 [8]. The investigators speculated if women with endometriosis "may have an incidence or a natural course of allergic, autoimmune or neoplastic diseases that are different from the general public" and in recent years several investigators have indeed reported that women with

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endometriosis seem to have an increased risk of developing allergic disorders [9–12]. Confirmation of a possible association could be a valuable step towards elucidating the pathophysiology of endometriosis.

Therefore, the purpose of this paper was to review the existing literature on the association between endometriosis and allergic disorders.

### *Hypersensitivity and allergic reactions*

Allergic disease is a common cause of chronic illness in developed countries, and its prevalence seems to be rising [13]. In a Swedish study the rate of self reported food allergy in the age group 20–44 was 25% and symptoms were more common in women than in men (28% and 21% respectively  $p < 0.1$ ) [14]. Another study conducted in Germany found the lifetime prevalence of medically diagnosed allergic disease to be 37.3% (95% confidence interval (CI): 33.2–41.7) among women in the age 18–29 years and for women between 30 and 39 years the prevalence was 42.2% (95% CI: 37.2–47.4) [15].

Although allergy is a term commonly used to describe all sorts of unexpected reactions in the skin and mucous membranes, type I allergy – immediate type hypersensitivity – is a distinct immunologic reaction, mediated by specific IgE antibodies bound to the surface of mast cells and basophils [16]. See Supplemental material on the pathophysiology of type 1 allergies.

Typical symptoms and manifestations of type I allergic disease includes asthma, rhino-conjunctivitis, gastrointestinal symptoms and characteristic skin lesions (urticaria).

It is important to distinguish between different types of allergic reactions, as the immunological effector mechanisms are different. The type 1 allergy, immediate hypersensitivity, is an allergic reaction due to the production of IgE antibodies against otherwise harmless antigens. The type IV or delayed type hypersensitivity involves antigen specific T-cells, and clinically presents itself as contact dermatitis [17]. Eczema however can also be present without any allergy as seen in irritant/toxic contact dermatitis, atopic dermatitis and dyshidrotic eczema [17,18].

### **Materials and methods**

The conduct and report of this review is based on the guidelines for the preferred reporting of systematic reviews and meta-analyses (PRISMA) [19], but was not preceded by a review protocol.

#### *Search strategy*

We performed a systematic literature search in PubMed and Embase for relevant studies published in the period 1980–January 2014. The search was made independently by two of the authors, HFB and UBK. For the database searches, the search terms “hypersensitivity” and “endometriosis” were used as Mesh/Emtree terms. To be certain that new, non-indexed studies were included, the search was expanded to include free text terms. Citations within the retrieved publications were examined for additional relevant articles.

#### *Study selection criteria*

The titles and abstracts were screened for the study design and measures of outcome and exposure. The included studies had to encompass a study group of women with a diagnosis of endometriosis and with manifestations of allergic disease, compared to a reference/control group. The studies had to be published as full-length articles in English. After these criteria were applied, five studies were found to be relevant for this review.

#### *Quality assessment and data extraction*

The Newcastle-Ottawa scale was used for assessing the quality of the included case–control studies. The studies were judged on the three perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the exposure. The studies were scored independently by HFB and UBK and discussed where inconsistency occurred. Because of the heterogeneity of the included studies we did not deem a meta-analysis suitable and a principal summary measure cannot be found. The articles considered relevant were critically read in full and were evaluated. Data were extracted using a data extraction form covering eligibility, population and setting, methods, participants, outcomes, exposures, results and applicability.

#### *Excluded measures of allergic disease*

The two studies [9,11] included chemical intolerance as a single measure of allergic disease. The aetiology of MCS is however unknown, widely debated, and will therefore not be included or further discussed in this review.

### **Results**

A flow diagram of the systematic search is shown in Fig. 1. A total of 316 papers were retrieved from the database searches. Of these, 310 did not meet the inclusion criteria. Six articles [9–12,20,21] were critically read in full text. One study was excluded [20] because the main investigation was not of allergic disease in women with endometriosis, but rather the prevalence of a genetic polymorphism, suspected to be associated to allergy. The remaining five articles were identified as relevant, in order to review the association between endometriosis and type 1 allergies (immediate type hypersensitivity). They are presented in Table 1 and discussed below.

#### *Asthma and endometriosis*

Sinaii et al. [12] found the asthma prevalence to be 12% among women with endometriosis compared to 5% for the general female population of the United States (US). Both Lamb et al. [9] and Nichols et al. [11] found that women suffering from endometriosis were twice as likely to report asthma (relative risk (RR) 2.16 and 2.37, respectively), although none of these reached statistical significance. Similarly Matalliotakis et al. [10] reported asthma prevalence to be higher in women suffering from endometriosis; (9% compared to 4.3% of the women in the control group, odds ratio (OR) 2.22 (95% CI: 1.20–4.12) ( $p = 0.038$ )).

In contrast Ferrero et al. [21] found no association when investigating asthma prevalence in women with endometriosis compared to the controls (4.9%, 95% confidence interval (CI): 3.1–7.3 and 5.3%; 95% CI: 3.4–8.0, respectively, ( $p = 0.781$ )). The investigators did not observe statistically significant differences in asthma prevalence among women with mild stage disease and severe stage disease of endometriosis (rAFS stage) ( $p = 0.413$ ), or when comparing asthma severity in women with and without endometriosis ( $p = 0.958$ ).

#### *Hay fever/allergic rhinitis of the sinus and endometriosis*

Lamb et al. [9] found hay fever to be reported three times more often among women with endometriosis compared to controls (RR 3.15,  $p < 0.02$ ), while Nichols et al. [11] found an RR of 2.08 ( $p < 0.02$ ) for hay fever among cases. Matalliotakis et al. [10] reported an OR of 23.32 (95% CI 9.42–57.73,  $p < 0.001$ ) indicating a significantly higher risk of allergic rhinitis among women with

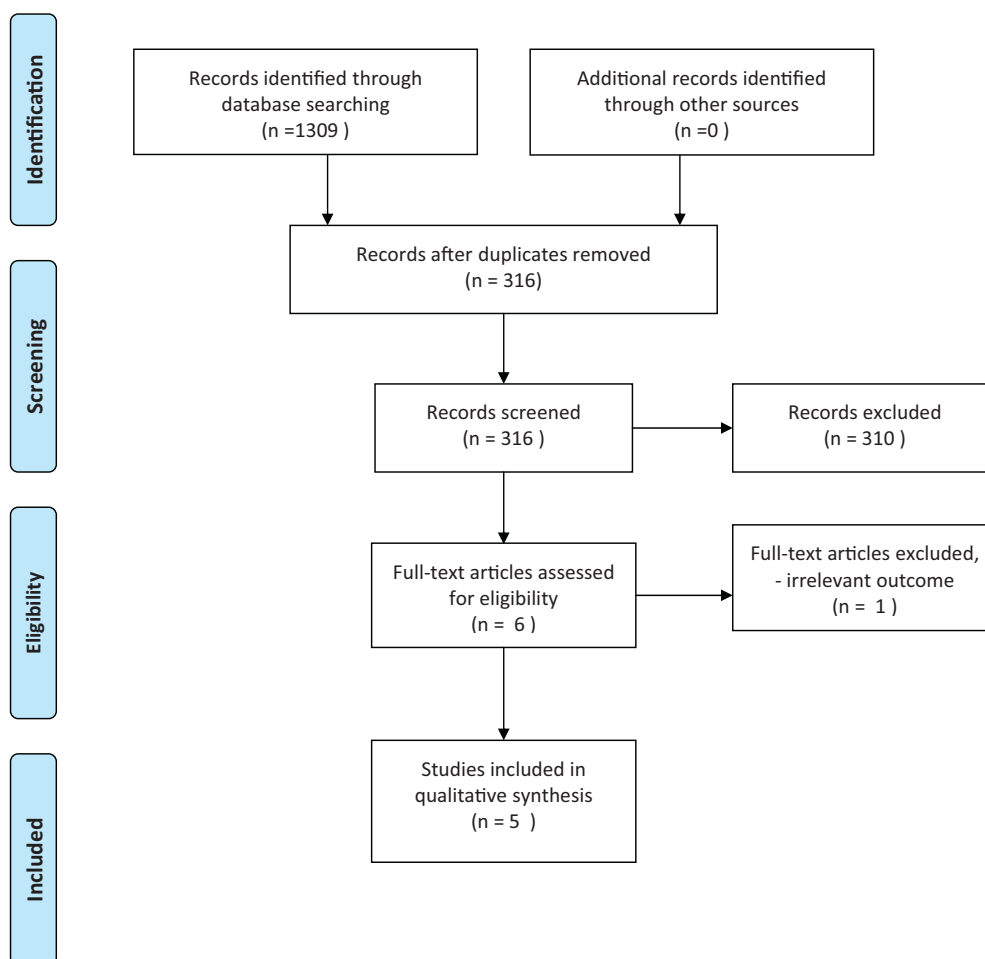


Fig. 1. PRISMA flowchart of the search and selection of the included studies.

endometriosis. The other 2 studies [12,21] did not comment on hay fever or allergic rhinitis.

#### Eczema and endometriosis

Three studies reported results on the risk of eczema among women with endometriosis. Women with endometriosis were found to have a significantly higher risk of suffering from eczema, compared to controls (RR 4.59  $p = 0.029$ ) [9]. Nichols et al. [11] also reported an increased risk of eczema (RR 2.37), but this was not statistically significant. Sinaii et al. [12] observed a prevalence rate of 15% among women with endometriosis. The observed rate was not compared to the prevalence of eczema in the general American female population.

#### Food sensitivities/intolerance (food allergy) and endometriosis

The risk of food sensitivities/intolerances was only investigated by two studies which found women with endometriosis significantly more at risk of food sensitivities; RR of 3.21 ( $p = 0.035$ ) [9] and food intolerances RR 2.10 ( $p < 0.02$ ) [11].

#### Miscellaneous other allergies and endometriosis

In Sinaii et al.'s study [12], all women reporting at least one allergy to either pollen, dust, trees, paint, grasses, cigarette smoke, perfumes/fragrances, cleaning products, foods or environmental chemicals were considered to have allergies. All in all 61% of

women suffering from endometriosis reported allergies compared to 18% of the general US female population ( $p < 0.001$ ). Matalliotakis et al. [10] included "other allergies" where allergies to dust, pollens, and trees, cleaning products, foods and environmental chemicals were included. The OR for other allergies were found to be 2.2 (95% CI 1.20–4.12). Allergy to medication was reported with an OR of 4.66 (95% CI 1.96–5.13) [10]. None of the other studies commented on drug allergies.

#### Relatives to women with endometriosis and their risk of allergic manifestations

Two studies reported on the risk of allergies among the family members of women suffering from endometriosis. Food sensitivities, eczema and hay fever, but not asthma, were found to occur significantly more frequently among family members both affected by endometriosis and allergic manifestations [9]. In accordance with these findings Matalliotakis et al. [10] reported allergic disease to be more common among the families of women suffering from endometriosis with or without additional allergies compared to the control group. For a 1st degree relative the OR for allergic manifestations were 8.32 (95% CI: 4.20–16.50) and 8.82 (95% CI: 5.27–14.79) ( $p < 0.0001$ ), respectively [10]. It is not known whether these women with endometriosis reporting a positive family history of allergic disorders also demonstrated a concurrent family history of endometriosis.

In conclusion four of the five included studies reported a positive correlation between endometriosis and allergic

**Table 1**  
Summary and quality scores of the studies.

| Study                     | Year | Study population                                                                                                                                                            | n    | Outcome measures                                                                                                                                                      | Evidence level | Results                                                                                                                                                                                                                                 | NOS score | Risk of allergic manifestations     |
|---------------------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------------------------------|
| Lamb et al. [9]           | 1986 | Case–control study. Cases (n = 43) women with endometriosis (The US Endometriosis Association) and with family members with endometriosis. Controls:(n = 43) female friends | 86   | Diagnose of asthma, eczema or hay fever. Family/self history of food sensitivities.                                                                                   | III            | Significantly higher frequency of eczema, hay fever, and food sensitivities among cases. All conditions occurred significantly more frequent among family members of cases, except for asthma.                                          | 1         | Increased risk of allergic disease. |
| Nichols et al. 1987 [11]  | 1987 | Case–control study. Cases (n = 88) women endometriosis. Controls (n = 88) female friends.                                                                                   | 176  | Symptoms of food sensitivities, eczema, asthma, hay fever.                                                                                                            | III            | Overall relative risk (RR) of 1.95 for allergic manifestations for cases compared to controls.                                                                                                                                          | 1         | Increased risk of allergic disease. |
| Sinaii et al. [12]        | 2002 | Cross-sectional survey. All women were members of the United States (US) Endometriosis Association.                                                                         | 3680 | Rates on allergies, asthma and eczema compared to the general female population of USA.                                                                               | III            | Asthma and allergy rates were significantly higher among women with endometriosis than the US female population.                                                                                                                        | NA        | Increased risk of allergic disease. |
| Ferrero et al. [21]       | 2005 | Cases (n = 467) Women with surgically and histologically confirmed endometriosis. Controls (n = 412) in surgery for benign gynaecological disorders.                        | 879  | Asthma prevalence and severity.                                                                                                                                       | III            | Asthma prevalence and severity similar in cases and controls.                                                                                                                                                                           | 6         | No increased risk of asthma.        |
| Matalliotakis et al. [10] | 2012 | Cases (n = 501) with surgically confirmed endometriosis. Controls (n = 188) with tubal or male factor infertility, but without endometriosis.                               | 689  | Allergy on medications, complaints of sinus or perennial allergic rhinitis, asthma, family history of allergic disease, and correlation with stages of endometriosis. | III            | Significantly higher prevalence of allergies on medications, allergic rhinitis, asthma and a positive family history of allergies among cases. No significant difference detected between allergic disease and stages of endometriosis. | 5         | Increased risk of allergic disease. |

manifestations [9–12], with investigators reporting an OR of 4.28 (95% CI: 2.93–6.27) [10] for women with endometriosis and a positive history of allergies. Nichols et al. [11] found that cases had an overall relative risk (RR) of 1.95 for allergic manifestations compared to controls, but not all conditions investigated contributed at a statistically significant level. Equivocal results were found on asthma prevalence.

### Quality of the studies included

The Newcastle-Ottawa scale is a method for assessing the quality of observational and non-randomized studies by using a star system. The NOS ranges from zero and up to nine stars. Studies were scored on the following criteria: quality of selection, comparability, and exposure of the study participants. This method was used for assessing the quality of the four case–control studies included in this review [9–11,21]. The quality of the studies, using the NOS, ranged widely from 1 star to a total score of 7 stars (Table 1). In studies where questionnaires were sent to participants [9,11,12], the reply rate was low. Nichols et al. [11] had a respond rate of 48% while 82% of women with endometriosis responded in the study by Lamb et al. [9] but only 65.2% of the friends (controls). Sinaii et al. [12] reported that approximately 55% of the women contacted responded. Due to time and budgetary constraints however, only 4000 of the responses were analysed. 320 of these were excluded, as their diagnosis of endometriosis had not been surgically confirmed. As the nature of the non-responders has not been evaluated, the low response rate is problematic, as they may differ from the rest of the group (the responders).

External validity could be compromised due to selection bias. The quality of case and control selection was wide-ranging

between studies, as an adequate case definition requires validation. To ensure an exact diagnosis of endometriosis, it usually needs to be confirmed by laparoscopy or at least by ultrasound for ovarian endometriosis. Three studies [9,11,12] found their participants/cases among the members of the US Endometriosis Association. One of these studies [9] failed to mention whether the diagnosis was confirmed by surgery, while the other two studies specifically stated that all of their cases reported were being diagnosed via laparoscopy or laparotomy. In the remaining studies [10,21] the diagnosis of endometriosis was confirmed surgically by either the investigators themselves or via patients' charts.

Further, in case–control studies the question of whether the cases were representative of all cases within the population (generalisability) should always be considered. When enrolling patients from the Endometriosis Association, one should consider that the women signing up for membership in an association could indicate a selection bias. They may be more troubled by their disease, have higher socioeconomic status, and be more aware of new treatments. In either case the association found might not be generalised, thereby limiting the external validity. Likewise, selecting cases enrolled from hospitals or clinics could also represent more severe cases of endometriosis.

Selecting controls also introduces a risk of selection bias. Two studies recruited hospital controls [10,21], but only the former study ruled out endometriosis. In the remaining studies, female friends were used as controls [9,11], because friends tend to be similar in lifestyle and socioeconomic background. A problem using friends as controls however, is the occurrence of over-matching. In both the studies 16% of controls reported endometriosis, and endometriosis was not ruled out in the remaining participants.

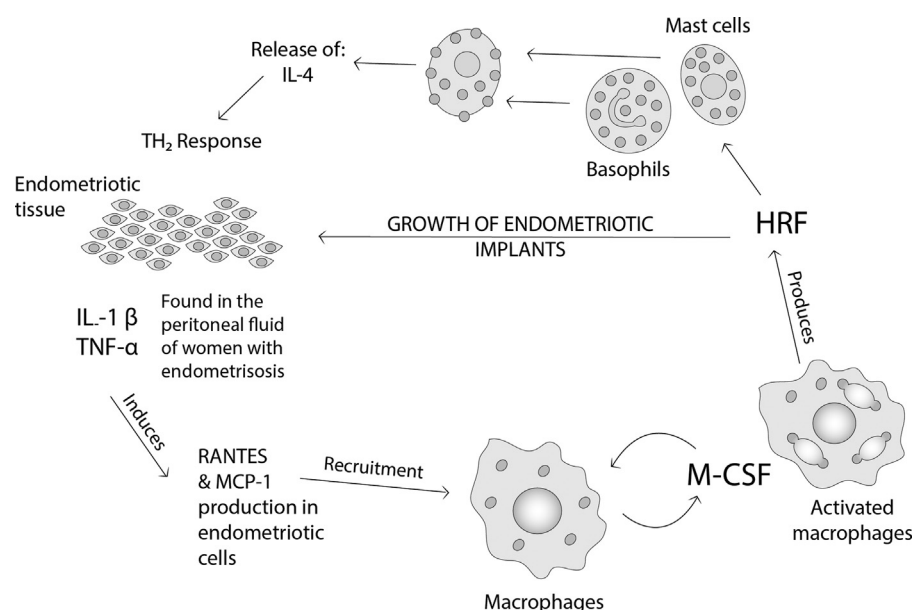


**Fig. 2.** The possible interaction between immediate type hypersensitivity reaction and endometriosis. Macrophage-colony stimulating factor (M-CSF) produced by macrophages autoinduces survival, proliferation and activation. Histamine releasing factor (HRF) induces production and release of IL-4 from mast cells and basophils. This could favour a Th2 response and the development of allergies (for details, please see [discussion and Supplemental material](#)).

Many of the studies did not report on control measures of potential confounders. Some included tables providing an overview of various sociodemographic characteristics of the study groups [9,11,21]. The investigators concluded that the participants were similar for the majority of the selected demographic characteristics ( $p > 0.05$ ). Only stating that demographic differences were not statistically significant however is not enough for establishing comparability as the NOS scale requires potential confounders to be adjusted for, or the participants to be matched in the design. Confounding factors potentially influencing the association between endometriosis and allergy therefore are not adjusted for, ultimately limiting the comparability of the study groups.

Verification of the level of exposure was overall poor. In three of the studies [9–11] a diagnosis of allergic disease was ascertained by questionnaires. Only in one study [21] was the structured interviewer blinded to case–control status as participants were interviewed on asthma prevalence before surgical evaluation and confirmation of endometriosis.

In the cross sectional study [12], data on the diagnosis of endometriosis, allergies, asthma and eczema were obtained from self-administered questionnaires. Allergies and asthma prevalences were subsequently compared to the rates in the general female population of the US, but were not restricted to women of the reproductive age.

## Discussion

In summary, four of five studies found an association between endometriosis and increased risk of allergic disorders, whilst one study reported no increased risk of asthma for women suffering from endometriosis. The methodological quality of the studies, however, varies greatly which evidently could mean that the association between endometriosis and allergic disorders were overestimated. The terminology used to characterise allergy and allergy-like reactions was not consistently defined. None of the studies linking allergic disease to endometriosis provided a definition of allergy, nor was the type of allergy investigated or how it was diagnosed described. One study [10] pointed out that in

their investigation, a physician diagnosed allergy, as the data was obtained from the patient charts, but they did not elaborate further on the diagnostic criteria.

To date, no in vivo or in vitro test exists that can give a reliable diagnosis of clinical allergy [22]. Skin prick test and assays to detect allergen specific IgE will only reveal if the patient is sensitised [22–24]. The golden standard for diagnosing type I allergy is direct allergen challenge tests, which can validate a skin prick test or specific IgE assays [23,24]. Self-reported surveys studies/questionnaires on the occurrence or severity of the allergic manifestations, which all of the studies were based on, have limitations as misinterpretation of questions and recall bias can compromise the results. For instance, in studies of food allergy, the prevalence based on self-reported symptoms was several fold higher compared to when the diagnosis was based on prick test, IgE levels with symptoms or the double blind placebo controlled food challenge (DBPCFC) [23].

All of the studies included asthma as a measure of allergic disease, but none of the investigators elaborated on whether the asthma had an allergic origin or was exercise induced. Furthermore, there are problems concerning the diagnosis of eczema, which three of the studies [9–11] referred to as an allergic manifestation. Allergic disease can indeed manifest itself as eczema, but eczematous skin disorders are not type I allergies but type IV allergies (except for protein contact dermatitis) and immunologically the pathophysiology of these eczematous skin disorders differs from the other allergic manifestations in the above mentioned studies.

Food sensitivities/intolerances were used as a measure of allergic disease in two of the studies [9,11], though this is a term that includes disorders of non-allergic pathophysiology. An example could be an individual with intolerance for milk due to an inability to digest lactose [23] or an individual with gluten intolerance which is caused by IgA or IgG against gluten [25]. Lactose deficiency is not an allergic condition where lactose is the allergen, but caused by the lack of an enzyme (lactase) resulting in abdominal pain and diarrhoea, and gluten intolerance is an inflammatory condition in the intestines also resulting in abdominal cramps and diarrhoea, which are the common symptoms of food allergy. Clinically these conditions may seem

indistinguishable and lactose intolerance testing or intestinal biopsies are needed to confirm the diagnosis. Abdominal cramps may also be the symptoms of endometriosis and this could influence the results of the studies in the cases where the diagnosis of endometriosis was not confirmed laparoscopic or surgically.

A common pathophysiology between allergy and endometriosis could be the pro-inflammatory cytokines accompanying allergic inflammation (see Supplemental material on the pathophysiology of type 1 allergies), which has also been found in endometriotic tissue. The studies made on the peritoneal fluid of women with endometriosis have shown an increased concentration of leukocytes, macrophages and lymphocytes [3,26]. A shift in the balance between the Th1 and Th2 response, toward the Th2 response [27], which favours the development of allergies [28] is also seen. The pathophysiology behind the association between endometriosis and allergy could be as illustrated in Fig. 2.

Activation of peritoneal macrophages has been suggested as a central contributor to the pathogenesis of endometriosis, as women with endometriosis demonstrated increased secretion of growth factors and pro-inflammatory cytokines in the peritoneal fluid [29,30]. The TNF- $\alpha$  and IL-1 $\beta$ , both macrophage-derived cytokines found in the peritoneal fluid of women with endometriosis, stimulate the synthesis of RANTES (regulated on activation, normal T cell expressed and secreted) and MCP-1 (monocyte chemotactic protein-1) in endometriotic cells [31,32]. The RANTES and MCP-1 exert their function on the recruitment of macrophages into endometriotic implants, which could be central in the HRF production [33,34]. The HRF plays a role in the allergic inflammation inducing IL-4 and IL-13 production [35,36]. Likewise, numerous activated mast cells have been found in endometriotic tissue samples [37] and IL-4, a secretory product of mast cells and basophils, has been found in increased concentrations in endometriotic tissue [28,38]. The IL-4 may stimulate proliferation of the endometriotic stromal cells besides acting as the key cytokine in the development of the Th2 response.

Thus, ectopic endometrial cells contribute to cytokine production in the peritoneal cavity. The cytokine production from endometriotic implants could serve as an allergenic factor, where activated macrophages are precursors of a cascade where the final production of Th2 cytokines could perpetuate a hypersensitivity reaction and thereby favour development of allergies.

One way to investigate this hypothesis is through a prospective observational study on who developed allergies and/or endometriosis, and the order of these occurrences. The difficulties concerning diagnosing both conditions would be a challenge however, as the time between onset of symptoms and subsequently a confirmed diagnosis of endometriosis may be as long as 6 or more years [1,7].

In conclusion, this systematic review illustrates that the existing literature on endometriosis and allergy is sparse. It is further hampered by the lack of definitions on allergic manifestations, leading to ambiguous conclusions, which makes it difficult to draw a firm conclusion on the relationship between these two disorders. However, overall the literature suggests that the risk of allergic manifestations among women with endometriosis is increased compared to the controls. If allergy and endometriosis are closely related, this will give further insight into the pathophysiology and hopefully in the future point to preventions and/or better treatments for endometriosis. Therefore, more studies are required to confirm or reject a possible relationship between endometriosis and allergy.

## Conflict of interest

The authors report no conflict of interest.

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## Role of authors

All authors (HFB, CV, UBK) were involved in the initial conception and design. HFB and UBK each performed the literature search, extracted the data separately, and discussed the quality assessment of the included studies where inconsistency was found. HFB wrote the initial draft of the manuscript. All authors contributed to the critical revision of the manuscript. We confirm that the order of authors listed in the manuscript has been approved by all of us.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejogrb.2014.04.025>.

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