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Hypothetical roadmap towards endometriosis: prenatal endocrine-disrupting chemical pollutant exposure, anogenital distance, gut-genital microbiota and subclinical infections

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BACKGROUND: Endometriosis is a gynaecological hormone-dependent disorder that is defined by histological lesions generated by the growth of endometrial-like tissue out of the uterus cavity, most commonly engrafted within the peritoneal cavity, although these lesions can also be located in distant organs. Endometriosis affects ~10% of women of reproductive age, frequently producing severe and, sometimes, incapacitating symptoms, including chronic pelvic pain, dysmenorrhea and dyspareunia, among others. Furthermore, endometriosis causes

infertility in ~30% of affected women. Despite intense research on the mechanisms involved in the initial development and later progression of endometriosis, many questions remain unanswered and its aetiology remains unknown. Recent studies have demonstrated the critical role played by the relationship between the microbiome and mucosal immunology in preventing sexually transmitted diseases (HIV), infertility and several gynaecologic diseases.

OBJECTIVE AND RATIONALE: In this review, we sought to respond to the main research question related to the aetiology of endometriosis. We provide a model pointing out several risk factors that could explain the development of endometriosis. The hypothesis arises from bringing together current findings from large distinct areas, linking high prenatal exposure to environmental endocrine-disrupting chemicals with a short anogenital distance, female genital tract contamination with the faecal microbiota and the active role of genital subclinical microbial infections in the development and clinical progression of endometriosis.

SEARCH METHODS: We performed a search of the scientific literature published until 2019 in the PubMed database. The search strategy included the following keywords in various combinations: endometriosis, anogenital distance, chemical pollutants, endocrine-disrupting chemicals, prenatal exposure to endocrine-disrupting chemicals, the microbiome of the female reproductive tract, microbiota and genital tract, bacterial vaginosis, endometritis, oestrogens and microbiota and microbiota–immune system interactions.

OUTCOMES: On searching the corresponding bibliography, we found frequent associations between environmental endocrine-disrupting chemicals and endometriosis risk. Likewise, recent evidence and hypotheses have suggested the active role of genital subclinical microbial infections in the development and clinical progression of endometriosis. Hence, we can envisage a direct relationship between higher prenatal exposure to oestrogens or estrogenic endocrine-disrupting compounds (phthalates, bisphenols, organochlorine pesticides and others) and a shorter anogenital distance, which could favour frequent postnatal episodes of faecal microbiota contamination of the vulva and vagina, producing cervicovaginal microbiota dysbiosis. This relationship would disrupt local antimicrobial defences, subverting the homeostasis state and inducing a subclinical inflammatory response that could evolve into a sustained immune dysregulation, closing the vicious cycle responsible for the development of endometriosis.

WIDER IMPLICATIONS: Determining the aetiology of endometriosis is a challenging issue. Posing a new hypothesis on this subject provides the initial tool necessary to design future experimental, clinical and epidemiological research that could allow for a better understanding of the origin of this disease. Furthermore, advances in the understanding of its aetiology would allow the identification of new therapeutics and preventive actions.

Key words: endometriosis / anogenital distance / chemical pollutants / prenatal exposure to endocrine-disrupting chemicals / female genital microbiome / microbiota-immune system interactions

Introduction

Endometriosis is a common gynaecological hormone-dependent disorder, defined by histological lesions generated by the growth of endometrial-like tissue (glands and endometrial stroma) out of the uterine cavity, most commonly engrafted within the peritoneal cavity (i.e. in the peritoneum wall, ovaries, rectosigmoid colon and bladder) although it can also be located in distant organs, such as the lung, liver, pleura, diaphragm, eye and brain. Different types of endometriosis include superficial peritoneal endometriosis, ovarian endometriomas, deep infiltrating endometriosis (DIE) and extragenital endometriosis (Vercellini *et al.*, 2014; Zondervan *et al.*, 2018).

Endometriosis has a remarkable impact on women's healthcare and quality of life, because it usually causes severe symptoms, including chronic pelvic pain, dysmenorrhea and dyspareunia, among others (Jones *et al.*, 2004; Denny and Mann, 2007; Vercellini *et al.*, 2014; Schliep *et al.*, 2015; Aerts *et al.*, 2018; Zondervan *et al.*, 2018; As-Sanie *et al.*, 2019). It is estimated that endometriosis affects approximately 176–200 million women worldwide, more than 10% of women of reproductive age (As-Sanie *et al.*, 2019), which can reach up to 40% of women aged 18–44 years and undergoing pelvic surgery (Buck Louis *et al.*, 2011; Peterson *et al.*, 2013). The annual incidence rate, from 1987 to 1999, in US women aged >15 years was 187 per 100 000, which peaked at ages 25–34 years (380–417 per 100 000) (reviewed by Shafrir *et al.*, 2018), was 350 per 100 000 in Germany (from 2004–2008) (Abbas *et al.*, 2012) and was 108 per 100 000 in Swedish women aged 15–50 years (Gao, Allebeck, *et al.*, 2019). However, from a population perspective, these numbers could be higher because not all affected women seek medical care or are diagnosed (Vercellini *et al.*, 2014; Zondervan *et al.*, 2018). The diagnosis of this pathology is difficult and most frequently requires invasive techniques, such as laparoscopic surgery for macroscopic observation and/or histological confirmation by biopsy (Vercellini *et al.*, 2014; Zondervan *et al.*, 2018; As-Sanie *et al.*, 2019). The annual medical cost of endometriosis in the USA was estimated to reach $22 billion in the year 2002 (Simoens *et al.*, 2007) and $69.4 billion in 2010 (Simoens *et al.*, 2012), due to its prevalence, the diagnostic techniques used and the insufficient availability of effective treatments (As-Sanie *et al.*, 2019).

Endometriosis is not caused by transformed cells; therefore, it is considered a benign disease. Nevertheless, endometriosis shares common characteristics with neoplasia, such as uncontrolled cell growth, invasion of adjacent tissues, defective apoptotic ability, a sustained local inflammatory response and altered angiogenesis, and it has been related to an increased risk of developing ovarian cancer (Wei *et al.*, 2011; Pearce *et al.*, 2012; Kim *et al.*, 2014; Kim, *et al.*, 2015; Machado-Linde *et al.*, 2015).

Although the aetiology of endometriosis remains largely unknown, it seems to have a multi-causal origin. Some hypotheses about the origin and pathogenesis of this disease include the following: adhesion and growth of endometrial tissue fragments after migration from the uterus toward the peritoneal cavity by a retrograde menstruation process (Sampson, 1927); coelomic metaplasia (peritoneal coelomic epithelium differentiates into endometrial-like cells); neonatal lymphatic or vascular metastatic spread of somatic stem cells and peritoneal implantation

that remains dormant until menarche; and abnormal embryonic remnant Müllerian ducts (from which the upper vagina, uterus and fallopian tubes develop) (Sourial *et al.*, 2014; Asghari *et al.*, 2018). Nevertheless, none of these theories has definitively demonstrated an absolute causal association with endometriosis (Vercellini *et al.*, 2014). For example, although retrograde menstruation is a frequent event, only 10% of women develop endometriosis; thus, other concurrent mechanisms need to be involved in its aetiology. In this sense, individual predisposition factors of genetic (Montgomery *et al.*, 2008; Borghese *et al.*, 2017; Matalliotakis *et al.*, 2017; Fung and Montgomery, 2018) and environmental origin (Hunt *et al.*, 2016; Smarr *et al.*, 2016; Cano-Sancho *et al.*, 2019; Wen *et al.*, 2019), together with a deficient or aberrant immune response (Asghari *et al.*, 2018; Riccio *et al.*, 2018; Symons *et al.*, 2018; Zhang, De Carolis, *et al.*, 2018), would allow the persistence and growth of endometrial tissue outside the uterus.

Many epidemiological studies have explored potential risk factors associated with endometriosis. As reviewed by Parasar *et al.* (2017), Parazzini *et al.* (2017) and Shafrir *et al.* (2018), consistent results have shown that higher parity and a higher body mass index (BMI) are inversely associated with endometriosis, while heavy menstrual cycles, early age at menarche and a lower BMI (Hediger *et al.*, 2005) are associated with a higher risk. Infertility (Peterson *et al.*, 2013; Gao, Allebeck, *et al.*, 2019), lower overall adiposity and adipose tissues concentrated below the waist (Backonja *et al.*, 2017) have also been reported as high risk factors. Additionally, inconsistent results have been reported on the association of endometriosis with alcohol and caffeine intake, smoking and physical activity (Heilier *et al.*, 2007; Matalliotakis *et al.*, 2008; Parasar *et al.*, 2017; Parazzini *et al.*, 2017; Saha *et al.*, 2017; Shafrir *et al.*, 2018; Hemmert *et al.*, 2019).

Presently, there is growing evidence linking endometriosis risk with high levels of endocrine-disrupting chemicals (EDCs) in women. This evidence has been reviewed and weighted by several authors, highlighting current knowledge gaps and future directions relative to endometriosis studies in adulthood (Guo *et al.*, 2009; Hunt *et al.*, 2016; Smarr *et al.*, 2016; Cano-Sancho *et al.*, 2019; Wen *et al.*, 2019). Industrial and household activity, agrochemical businesses and human pharmacological consumption produce a large environmental accumulation of EDCs, especially in the sewage network and, ultimately, in surface water, as is the case for alkylphenols (from detergents and surfactants), organochlorines (from insecticides), phthalates and bisphenol A (BPA), octylphenol and nonylphenol (from plasticisers), flame retardants, heavy metals (cadmium used in batteries), dioxins and several compounds contained in cosmetics, such as benzophenones and natural oestrogens and contraceptives, which are detected in surface water in ranges of ng/L to µg/L (Rahman *et al.*, 2009; Adeel *et al.*, 2017). Furthermore, it should be noted that humans are, in fact, exposed to a mixture of EDCs and the additive, synergistic, inhibitory and overall cumulative effects of multiple EDCs have not been empirically delineated (Gore *et al.*, 2015). Furthermore, there is a high concern about the growing experimental evidence that supports the theory of the 'foetal basis of adult disease' (Barker, 1990), which postulates that prenatal environmental exposure may be associated with the development of future diseases. Accordingly, estrogenic or anti-androgenic EDCs could induce significant alterations in prenatal development and the early post-natal periods of life, even at very low doses of exposure, and would be linked to the development of many chronic diseases (Street *et al.*, 2018), for example, breast cancer (Soto *et al.*, 2013; Paulose *et al.*, 2015; Scsukova *et al.*, 2016), diabetes (Howard, 2019), obesity (Braun, 2017), neurodevelopment (Braun, 2017), allergies (Berger *et al.*, 2019; Quirós-Alcalá *et al.*, 2019), endometriosis (Upson *et al.*, 2015), uterine fibroids (Katz *et al.*, 2016) and several reproductive alterations (Sifakis *et al.*, 2017) including during early puberty (Harley *et al.*, 2019; Lee *et al.*, 2019), among others (Paulose *et al.*, 2015; Prusinski *et al.*, 2016; Rashtian *et al.*, 2019). Hence, epidemiological studies of endometriosis have focused on risk factors directly or indirectly associated with prenatal exposures, e.g. maternal smoking (Vannuccini *et al.*, 2016; Gao, Scott, *et al.*, 2019), low birth weight (Missmer *et al.*, 2004; Borghese *et al.*, 2015; Shafrir *et al.*, 2018; Gao, Scott, *et al.*, 2019) and prematurity (Upson *et al.*, 2015; Vannuccini *et al.*, 2016), which have been associated with an increased endometriosis risk, although a lower risk association with maternal smoking (Buck Louis *et al.*, 2007) or no association with others prenatal factors has also been reported (Somigliana *et al.*, 2011; Wolff *et al.*, 2013). Those observations, and others that revealed the presence of ectopic endometrium in human foetuses (Signorile *et al.*, 2012) as well as a prenatal-induced endometriosis-like phenotype in mice (Signorile *et al.*, 2010; Koike *et al.*, 2013), support this theory (Wei *et al.*, 2016). The first historical human evidence was the increased risk of endometriosis found in the daughters of women who were administered diethylstilboestrol (DES) (Missmer *et al.*, 2004; Upson *et al.*, 2015), a potent synthetic oestrogen drug with endocrine-disrupting effects that was prescribed between 1947 and 1971 to millions of women worldwide to prevent miscarriage (Reed and Fenton, 2013; Wei *et al.*, 2016). More recently, a shorter female anogenital distance (AGD), an indirect and reliable biomarker of the prenatal hormonal milieu, including EDCs (Callegari *et al.*, 1987; Thankamony *et al.*, 2009, 2016; Liu *et al.*, 2014; Barrett *et al.*, 2018; Schwartz *et al.*, 2019), has been significantly associated with endometriosis (endometriomas, DIE or both) (Mendiola *et al.*, 2016), suggesting that certain *in utero* hormones or EDCs may cause female genital tract (FGT) alterations that could be relevant to develop endometriosis. To our best knowledge, there is still no epidemiological data linking those variables.

Finally, the explosive growth of knowledge about the human microbiome has led to the emergence of a new hypothesis posing an infectious origin of endometriosis. Accordingly, it could be promoted by certain, but yet undetermined, alterations of the healthy microbiota (gut, oral and/or FGT), which have recently been associated with endometriosis risk, likely by disrupting the microbiota-immune system tolerance, thus causing a subclinical inflammatory state that could allow endometriosis development (Kavoussi *et al.*, 2009; Laschke and Menger, 2016; Lin *et al.*, 2016; Khan *et al.*, 2018; Tai *et al.*, 2018; Thomas *et al.*, 2018).

Herein, we have aimed to merge rather large and speculative distinct areas into an aetiological roadmap to endometriosis based on emerging epidemiological and experimental evidence. Hence, we hypothesise that there may be a direct relationship between high prenatal exposure to environmental and/or pharmaceutical EDCs (phthalates, bisphenols, organochlorine pesticides, dioxin-like compounds and others) with a shorter AGD or other FGT alterations, which could favour frequent postnatal episodes of faecal microbiota contamination of the vulva and vagina, producing cervicovaginal (CV) microbial dysbiosis that sustains subclinical inflammation processes and a high risk of developing endometriosis.

Methods

Bibliography search strategy

A flowchart of the search strategy and selection of articles included in this work is shown in Fig. 1. We conducted a systematic search in PubMed. The search strategy included keywords related to the scientific literature that focused on studies containing research data that related endometriosis to the following: immune system alterations, the female AGD, prenatal risk factors, prenatal exposure to EDCs, prenatal exposure to EDCs and the AGD, postnatal exposure to EDCs, intestinal and FGT microbiota, dysbiosis of the FGT, bacterial vaginosis, endometritis, estrobolome, FGT subclinical infections, periodontitis and microbiota–immune system interactions. Specifically, the combinations of terms used for the literature search were the following (with '*n*' being the number of publications found for each combination of terms): 'Endometriosis and oestrogens' ($n = 1618$), 'Endometriosis and immune system' ($n = 989$), 'Endometriosis and risk factors' ($n = 1499$), 'Endometriosis and prenatal risk factors' ($n = 21$), 'Anogenital distance and endometriosis' ($n = 6$), 'Endocrine disruptors and endometriosis' ($n = 46$), 'BPA and endometriosis' ($n = 20$), 'Diethylstilboestrol and endometriosis' ($n = 82$), 'Dioxin and endometriosis' ($n = 136$), 'Hexachlorobenzene and endometriosis' ($n = 4$), 'Organochlorines and endometriosis' ($n = 68$), 'Pesticides and endometriosis' ($n = 47$), 'Phthalates and endometriosis' ($n = 24$), 'EDC and human prenatal exposure' ($n = 80$), 'Endocrine disruptors and AGD' ($n = 45$), 'Prenatal bisphenol A and AGD' ($n = 13$), 'Prenatal dioxins and AGD' ($n = 2$), 'Prenatal diethylstilboestrol and AGD' ($n = 3$), 'Prenatal hexachlorobenzene and AGD' ($n = 0$), 'Prenatal organochlorines and AGD' ($n = 9$), 'Prenatal pesticides and AGD' ($n = 16$), 'Prenatal phthalates and AGD' ($n = 14$), 'Estrobolome' ($n = 5$), 'EDCs and microbiome' ($n = 19$), 'Female genital tract microbiome and endometriosis' ($n = 5$), 'Female genital tract microbiome and dysbiosis' ($n = 99$), 'Microbiome and endometriosis' ($n = 17$) and 'Periodontitis and endometriosis' ($n = 10$).

Inclusion and exclusion criteria

The articles eligible for inclusion herein were those available online, written in English and published from 2000 until 2019 (20 years), although relevant related articles from earlier dates were also included. Given the amplitude of literature relative to certain areas, recent relevant reviews were selected to present the conceptual framework of our hypothesis. Additionally, reviews containing the meta-analysis of epidemiological studies conducted in women related to these areas were included. Consequently, some of the references analysed in selected reviews and meta-analyses were not cited here because their results were already implicitly considered. Other reviews or publications without new relevant results were excluded, as well as articles for which only the abstract was available but not the full text. We also excluded single case reports, letters to editors and papers displaying the development of new technical tools or testing of diagnostic and therapeutic tools. The population of interest was principally women, although some studies on animal models related to EDCs and the AGD, EDCs and microbiota–immune system interactions were also selected, given the absence of published results corresponding to long-term human studies on these issues. Hence, most articles based solely on data from male animal models were excluded. The same reason applied to the exclusion of most *in vitro* studies.

Selection procedure

Two authors (P.G.P. and A.J.R.A.) read the titles and abstracts independently to check the eligibility. The first search yielded 4897 results, with 3344 papers published in the selected period of time (2000–2019). After screening the titles and abstracts, 402 unique full-text articles (including 7 articles published before 2000) that met the eligibility criteria were downloaded and 83 articles reporting only male animal results, as well as others in which neither human female samples nor prenatal EDCs exposure were investigated, were also excluded. After reading the full text, the final number of eligible articles selected was 319. Next, those articles were used to establish the conceptual framework presented in the 'Introduction' section, as well as to present, weigh and discuss in the 'Results and Discussion' section the evidence related to the 'Proposed model of endometriosis development' and 'Future direction in endometriosis research' sections. Thus, the articles selected for this purpose were those that investigated the association between a high prenatal exposure to EDCs with alterations of the female AGD and those that investigated the association of endometriosis with the following: FGT immune dysregulation, EDCs, the AGD and alterations of oral, intestinal and genital microbiota.

Female Genital Tract Mucosal Immune Microenvironment

Recent studies of the FGT mucosal immune system have demonstrated the critical role that it plays in maintaining the balance between defence against infections and tolerance to microbiota as well as to both 'non-self' sperm and semi-allogeneic foetuses (Black *et al.*, 2000 and reviews by Pepe *et al.*, 2018 and Zhou *et al.*, 2018).

Different types of immune cells are scattered throughout the mucosal lamina propria, such as antigen-presenting cells (APCs) (macrophages, dendritic cells (DC) and B lymphocytes), innate lymphoid cells (ILC), NK cells, T cells (CD4+ and CD8+) and antibody-secreting plasma cells, among others (Fig. 2) (Hickey *et al.*, 2011; Zhou *et al.*, 2018).

Four types of myeloid-derived APCs have been identified in the CV mucosa, namely CV-Langerhans cells (located in the CV epithelium in homeostasis), $CD14^-$ DC, CD14+ DC and CD14+ macrophages (located in the lamina propria) (Duluc *et al.*, 2013). Mucosal DCs play an important role in maintaining microbiota tolerance because of their ability to detect, process and present microbial antigens to T lymphocytes (Anahtar *et al.*, 2015). In this regard, CV-Langerhans cells and $CD14^-$ DCs have gene expression profiles associated with tolerogenic or T_H2-inducing activity. In turn, B lymphocytes specifically recognise microbial antigens and differentiate into plasma cells that secrete IgM, IgA and IgG; the latter seems to be more abundant than IgA at this location (Crowley-Nowick *et al.*, 1995; Hickey *et al.*, 2011; Zhou *et al.*, 2018). IgG and IgA play crucial roles in mucosal immunity by neutralising the growth of microorganisms, thereby preventing adhesion and invasion of pathogens. Notably, the production of IgG and IgA in the FGT seems to be hormonally regulated

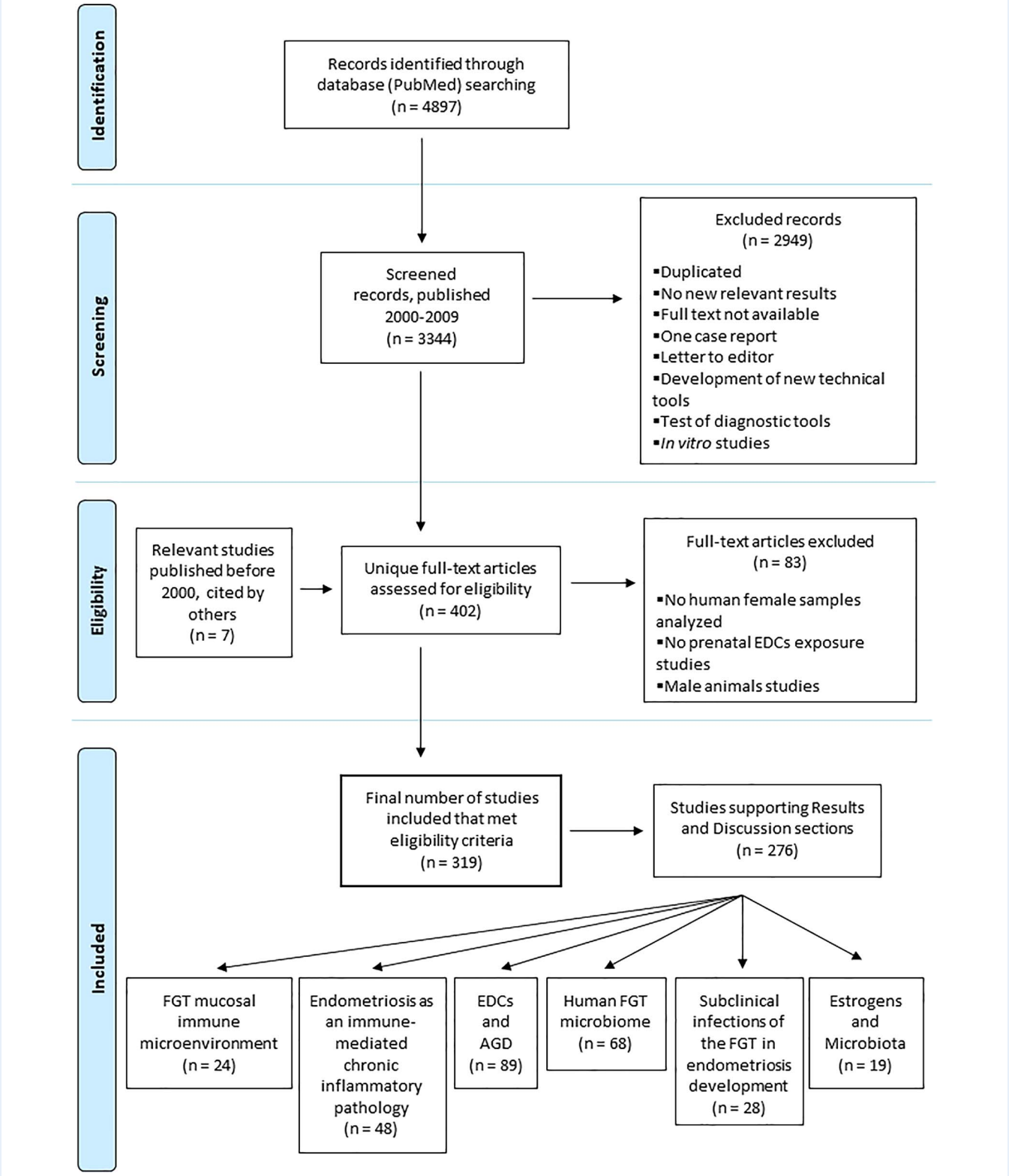

Figure 1 **Flowchart methodology for the search and selection of relevant articles.**

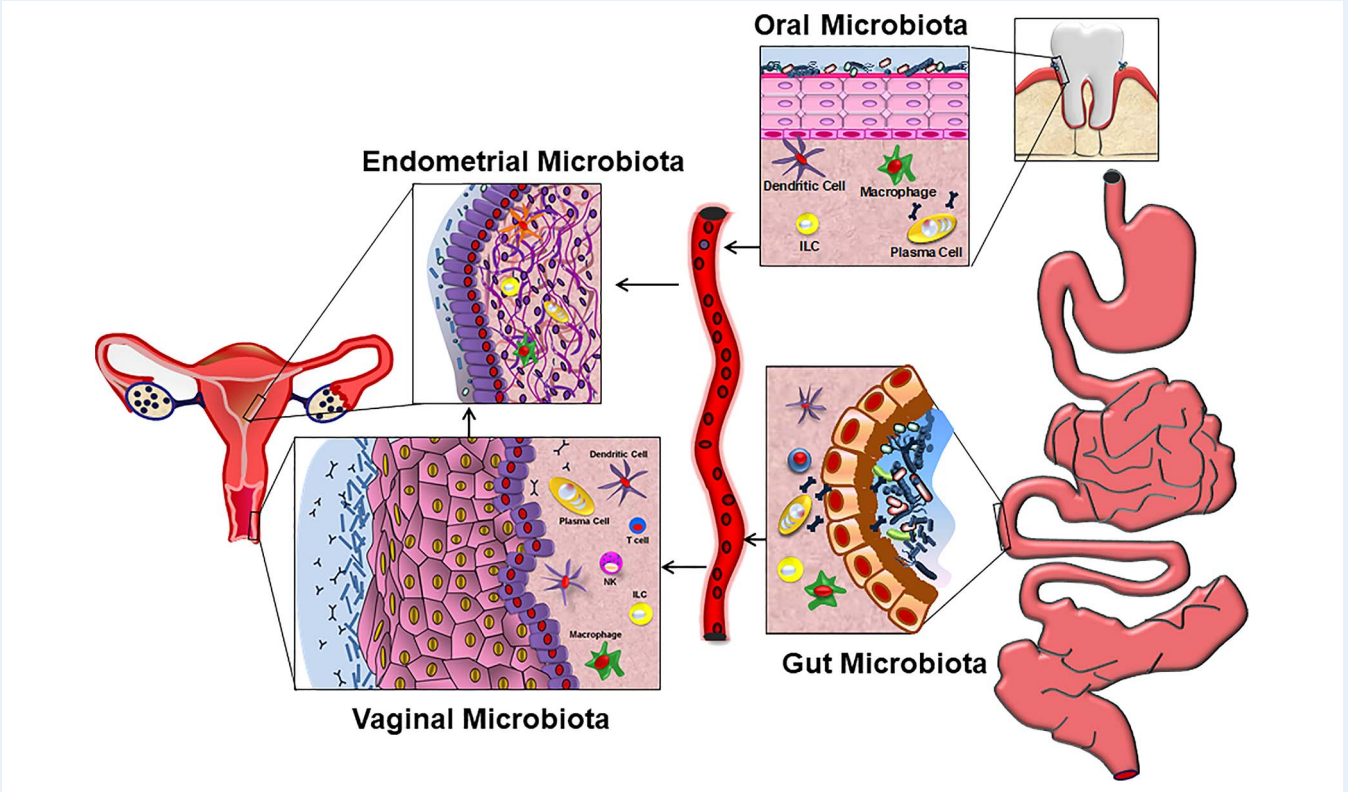

Figure 2 Potential sources of bacteria colonising the human female genital tract. The oral and intestinal microbiota can be translocated directly or indirectly through the lymphatic circulation, into the bloodstream, from where it can gain access to the mucosa of the FGT. The vaginal microbiome in homeostasis presents low diversity with a predominant presence of beneficial *Lactobacillus* species, which are tolerated by the mucosal immune system.

(Wira *et al.*, 2015; Zhou *et al.*, 2018). Human vaginal NK cells have a similar phenotype to that of peripheral blood NK cells (Mselle *et al.*, 2007). A significant number of CD4+ and CD8+ tissue-resident memory T cells are also located in the CV lamina propria. These cells rapidly secrete IFN-γ and induce epithelial cell secretion of chemokines CXCL9 and CXCL10, which activate the local endothelium to recruit certain types of immune cells. The cervix also contains many CD4+ (40%) and CD8+ (60%) T cells (effector and T effector memory) and, to a lesser extent, monocytes/macrophages, DCs, NK cells and B lymphocytes (Trifonova *et al.*, 2014). As a FGT tissue-specific function, macrophages, neutrophils and NK cells contribute to the physiological changes produced during the menstrual cycle through the synthesis of chemokines, proteases and angiogenic factors. The uterine lamina propria also contains macrophages, neutrophils, uterine NK (uNK) cells and characteristic lymphoid aggregates containing a core of B cells surrounded by CD8+ T cells and an outer layer of macrophages (Cousins *et al.*, 2016; Hickey *et al.*, 2011; Zhou *et al.*, 2018).

Innate lymphoid cells (ILC) are located in all tissues but are more abundant in mucosal tissues and barrier surfaces, especially in the gut lamina propria. Current studies of phenotypic and functional analyses of ILCs in the FGT mucosa are very scarce (Doisne *et al.*, 2015; Vacca *et al.*, 2015; Bartemes *et al.*, 2018; Filipovic *et al.*, 2018; Miller *et al.*, 2018). These cells lack the antigen receptor (TCR), express the IL-7 receptor (IL7Rα, CD127), maintain tissue homeostasis and initiate the immune response against infections. Three subpopulations functionally similar to CD4+T helper cells have been described: ILC1 cells that express the transcription factor T-bet and produce IFN-γ and TNF-α similar to T_H1 cells; ILC2 cells that express the transcription factor Gata3 and secrete amphiregulin and T_H2 cytokines, such as IL-4, IL-5 and IL-13; and ILC3 cells characterised by the expression of the RORγt transcription factor and secretion of IL-17A, IL-22, lymphotoxin and GM-CSF, similar to T_H17 lymphocytes. Hence, ILCs coordinate and polarise the initial response against infections or tissue injury, depending on the profile of tissue factors and cytokines present, with the main difference in the speed of the response with respect to the corresponding action mediated by specific adaptive immune cells (Eberl *et al.*, 2015a; Eberl *et al.*, 2015b; Serafini *et al.*, 2015).

Treg cells play an essential role in maintaining tolerance to the foetus (Aluvihare *et al.*, 2004), as well as controlling exaggerated immune reactions against intestinal microbiota, while effector T cells (T_H1, T_H2 and T_H17) are necessary to protect the mucosa from pathogens. Therefore, the mucosal balance between Treg and effector T cell subsets is essential to maintaining homeostasis (Pandiyan *et al.*, 2019). T_H17 and T_H1 are the most important mucosal effector T lymphocytes (Fig. 3D). Differentiation to T_H17 cells requires the presence of the transcription factor RORγt, which is involved in the production of IL-17 and the IL-23 receptor (Romagnani *et al.*, 2009; Buonocore *et al.*, 2010). In turn, T_H1 lymphocytes are characterised by expression of the transcription factor T-bet and are especially effective in combating

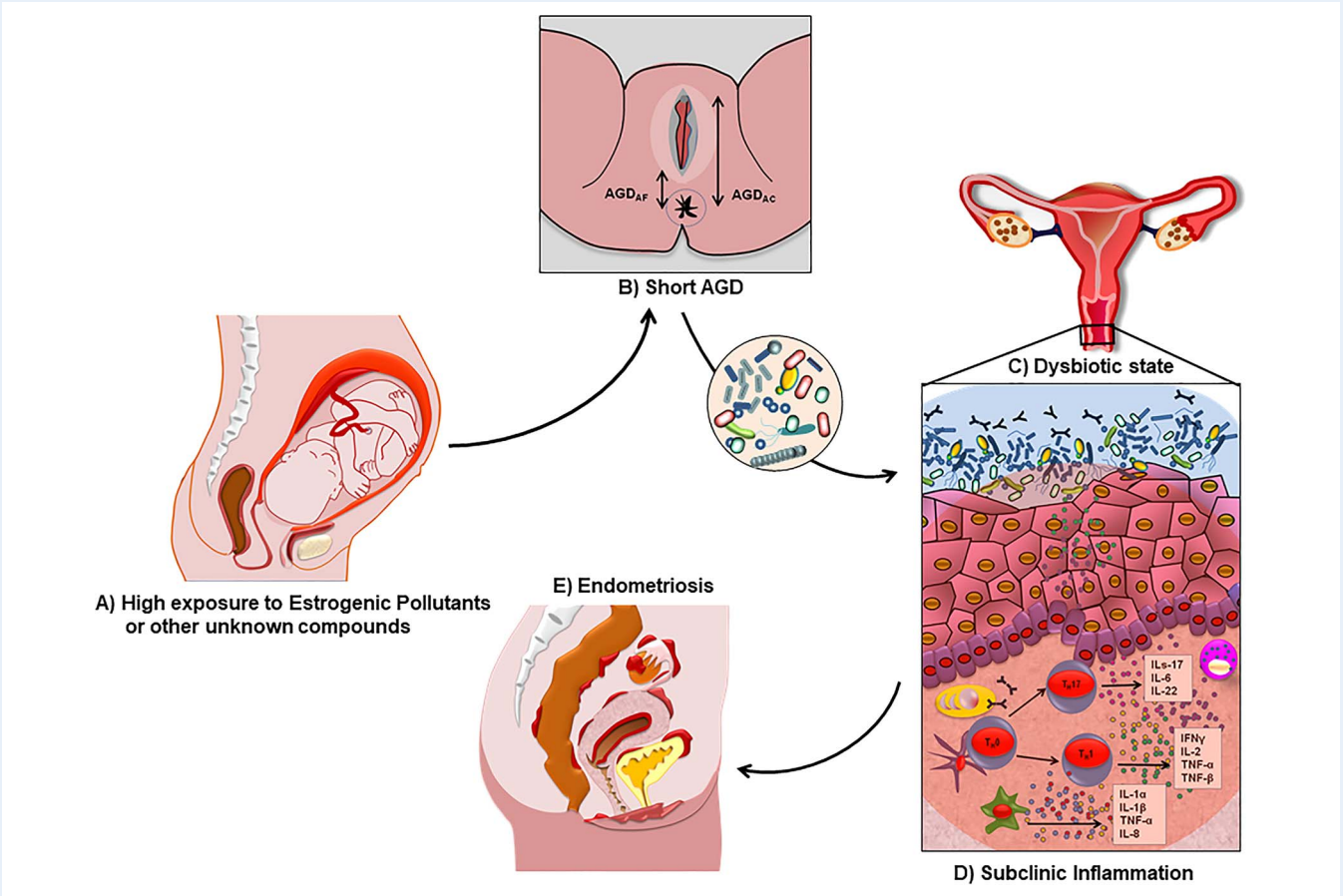

Figure 3 Model of the risk factors associated with the development of endometriosis. (**A**) A high level of EDC (mainly oestrogen-like compounds) exposure during the prenatal stage induces a shorter AGD (**B**) that could affect the physiological development of other sexual features and enhance future episodes of retrograde menstruation. (**C**) Additionally, during childhood, a short AGD would favour frequent faecal microbiota contamination from the anus toward the external and lower FGT (the vulva and vagina), producing early FGT dysbiosis (**D**), which could disrupt FGT antimicrobial defences and generate an initial subclinical inflammatory response mediated by pro-inflammatory cytokines produced mainly, although not exclusively, by macrophages, T_H1 and T_H17 cells. This immune dysregulated state could evolve into a long-term sustained immune activation, closing the vicious cycle responsible for endometriosis development.

virus and intracellular bacteria. Notably, differentiation to T_H1 or T_H17 lymphocytes depends on the presence of a specific local microbiota (Mao *et al.*, 2018).

These findings demonstrate the close relationship established between the microbiota and mucosal immune system to maintain homeostasis and protect against infections. However, studies on the relationships between the microbiota and FGT mucosal immune system are more scarce.

Endometriosis Is Considered as an Immune-Mediated Chronic Inflammatory Pathology

The main histopathological features associated with this disease are local inflammation and peritoneal fibrosis. Differences in invasive properties and resistance to apoptosis have been described between the endometrium of women with and without endometriosis, as well as between the ectopic and eutopic endometrium of patients, suggesting that the peritoneal inflammatory environment participates in the development of ectopic lesions (Vercellini *et al.*, 2014; Miller *et al.*, 2017; Asghari *et al.*, 2018; Klemmt and Starzinski-Powitz, 2018; Patel *et al.*, 2018; Zhang *et al.*, 2018a; Zondervan *et al.*, 2018). Although retrograde endometrial tissue in healthy women is usually cleared by peritoneal immune cells, endometriotic cells may evade immune surveillance and adhere onto peritoneum and other organs (Christodoulakos *et al.*, 2007).

Macrophages are key regulators of the immune response in infected, damaged or neoplastic tissues, where they must promote the appropriate response to restore homeostasis (Gordon *et al.*, 2014; Pepe *et al.*, 2018). Macrophages play an important role in endometriosis and constitute the predominant leukocyte population in the peritoneal fluid of affected women (Capobianco and Rovere–Querini, 2013; Cousins *et al.*, 2016). Recent studies have suggested that the inappropriate activity of macrophages is involved in the maintenance of auto-transplanted endometrial tissue in the abdominal cavity (Bacci *et al.*, 2009; Capobianco and Rovere-Querini, 2013; Shao *et al.*, 2016; Wu, Xie, *et al.*, 2017). Hence, alternative activation

of macrophages towards a tissue-repair phenotype (M2) would allow the survival, neovascularisation and growth of endometriotic lesions (Bacci et al., 2009; Capobianco and Rovere-Querini, 2013; Wu, Xie, et al., 2017; Duan et al., 2018; Sun et al., 2019). Additionally, other authors have described classical macrophage polarisation (M1) in the eutopic endometrium of patients with endometriosis with respect to healthy individuals (Takebayashi et al., 2015). Analysis of the molecular mechanisms that mediate the activation and polarisation of macrophages is necessary to understand the pathophysiology of endometriosis and allow the development of new medical treatments. Furthermore, dysfunctional NK cells (Elkabets et al., 2010; Kang et al., 2014; Yu et al., 2016), which express higher levels of inhibitory receptors (KIR) (Wu et al., 2000) and a lower number of activating receptors (KAR), down-regulate the phagocytic activity of macrophages and expression of scavenger receptors (Chuang et al., 2009) and induce Treg lymphocytes, whose inhibitory activity allows endometrial cells to escape from peritoneal immune surveillance (Christodoulakos et al., 2007; Gogacz et al., 2014; de Barros et al., 2017; Wang et al., 2017; Hanada et al., 2018). Additionally, the rapid increase in peritoneal myeloid-derived suppressor cells (MDSCs) in the presence of endometrium could be involved in the depressed immune response (Elkabets et al., 2010; Zhang et al., 2018b). Consequently, there is an increase in soluble mediators secreted by macrophages and other cells (Hassa et al., 2009; Mu et al., 2018; Nothnick and Alali, 2016; Rakhila et al., 2016), including TGF-β (responsible for post-surgical adhesions) (Choi et al., 2017; Hanada et al., 2018), IL-1β (induces COX-2 and VEGF expression, increasing angiogenesis) (McLaren, 2000; Huang et al., 2013), IL-8 (increases proliferation, migration, angiogenesis and survival of migrated endometrial cells) (Ulukus et al., 2009; Sikora et al., 2017), PGE_2 (induces oestrogen synthesis in collaboration with IL-4, inhibits apoptosis and increases the production of FGF-9) (Urata et al., 2013), MIF (increases the expression of VEGF, IL-8 and MCP-1 in endometriotic cells, induces angiogenesis and is a tissue remodelling agent) (Veillat et al., 2010), MCP-1 (increases monocyte recruitment) (Ulukus et al., 2009; Li et al., 2012; Gou et al., 2019), sICAM-1 (Kuessel et al., 2017), IL-6 (Li et al., 2017) (inhibits cytotoxicity mediated by NK cells (Kang et al., 2014)), IL-27 (triggers the secretion of IL-10 by T_H17 cells inducing the promotion of endometriosis) (Chang et al., 2017) and IL-32 (Lee et al., 2018), among others (Nothnick and Alali, 2016; Mu et al., 2018). Through the study of transcriptomes, the STAT proteins, SMAD transcription factors and Akt and MEK/ERK signalling pathways have been identified as central signalling regulators of the pathophysiological processes that lead to the development of endometriosis (Li et al., 2012, 2019; Matsuzaki and Darcha, 2015 and reviews by Aznaurova et al., 2014; McKinnon et al., 2016; Patel et al., 2018; Riccio et al., 2018).

Endocrine-Disrupting Chemicals and Anogenital Distance

As mentioned above, numerous cohort, cross-sectional and case–control studies conducted in patients with endometriosis have sought the association between EDC levels in women and endometriosis. Although some inconsistent results have been obtained, as new studies accumulate, evidence of an EDC–endometriosis association obtained in systematic reviews and meta-analyses of the available studies is increasing, as shown in Table I. Early on, Guo et al. (2009) reviewed the molecular biology and weighted the evidence on 17 epidemiological studies of the association between dioxins and endometriosis, concluding that no significant evidence supported a link between dioxin and endometriosis. More recently, Smarr et al. (2016) summarised the weight of evidence on the relationships between endometriosis and several persistent and non-persistent EDCs, concluding that the existing evidence supported a possible relationship between many EDCs and endometriosis, except for BPA and polybrominated diphenyl ethers (PBDEs). Furthermore, they discussed the key methodological challenges that preclude a more complete understanding of the literature, followed by suggestions to answer critical data gaps. An analysis of the association between phthalates and endometriosis conducted by an expert panel in the European Union rated the strength of epidemiological and toxicological evidence as 'low' and 'moderate', respectively (Hunt et al., 2016). Recently, Cano-Sancho et al. (2019) reported a significant but 'moderate evidence' of association between organochlorines and endometriosis by a meta-analysis of 17 studies, and Wen et al. (2019) also analysed and weighted the evidence of 30 studies conducted on EDCs and endometriosis (4 with BPA, 12 with PCBs, 8 with organochlorine pesticides (OCPs) and 6 with phthalates) and reported a significant association with all of them, except with BPA.

This association could likely be produced by the suggested potential of EDCs to modify the attachment and proliferation of endometrial (Kim et al., 2015) and endothelial cells (Bredhult et al., 2007), to increase reactive oxygen species generation and decrease expression of antioxidant enzymes (Cho et al., 2015), as well as to disrupt inflammatory and endocrine responses, as described from *in vitro* and murine experimental studies (Huang et al., 2017), as well as to modify the invasion parameters in endometriotic lesions in a rat model, increasing the expression of COX-2, VEGF and TNF-α (Chiappini et al., 2019).

Recently, a short anofourchettal distance (AGD_{AF}) in adults has been statistically associated with adult endometriosis (endometriomas, DIE or both) (Mendiola et al., 2016). Consequently, it has been proposed as a useful risk marker for clinical and epidemiology studies (Sánchez–Ferrer et al., 2017, 2019) (Table II). Hence, although the current level of evidence is insufficient, given the small number of studies and sample size, it will be of great interest to uncover the mechanisms underlying the association between the AGD and endometriosis.

The AGD is a sexual dimorphic anatomical characteristic, defined as the length from the anus to the genitals. In many species of mammals, including humans, the AGD is almost twice as long in males than in females both in childhood (Thankamony et al., 2009) and throughout life (Salazar-Martinez et al., 2004; Barrett et al., 2014; Kim, Lee, et al., 2014; Thankamony et al., 2016; Priskorn et al., 2018; Schwartz et al., 2019).

Studies in animal models have shown that the AGD at birth is directly related to intra-uterine hormonal exposure (Wolf et al., 2002; Dean et al., 2012). Thus, a higher content of androgens results in a longer AGD, while higher oestrogen or anti-androgen exposure is associated with a shorter AGD (Hotchkiss et al., 2007; Dean and Sharpe, 2013; Schwartz et al., 2019). Association with a shorter AGD in female animals has been reported for phthalates: di-ethylhexyl-phthalate (DEHP) (Brehm et al., 2018), a mixture (Zhou et al., 2017a; Repouskou et al., 2019), a mix of phthalates and alkylphenols (Patiño–García et al., 2018), BPA (Christiansen et al., 2014), butylparaben (Boberg et al., 2016), nonylphenol (Takagi et al., 2004), benzophenone

Table I Association between adult exposure to EDCs and endometriosis risk.

Meta-analyses

Reference	Epidemiological studies (*N*)	EDC types	EDC analysed (*N*)	Risk association odds ratio	Sample	Association	Weight (%)	Level of evidence
Cano-Sancho *et al.* (2019)	17	Organochlorines	Dioxins (10) PCBs (9) OCPs (37)	1.65; 95% CI (1.14, 2.39) 1.70; 95% CI (1.20, 2.39) 1.23; 95% CI (1.13, 1.36)	Serum (13) Blood (2) Fat (3)	Positive Positive Positive		**Moderate**
Wen *et al.* (2019)	30	Bisphenol A	BPA (4)	1.4; 95% CI (0.94, 2.08)	Serum (14) Urine (8) Fat (1)	NS	13.95	**Moderate**
		Polychlorinated biphenyls	PCBs (12)	1.58; 95% CI (1.18, 2.12)		Positive	30.4	
		Organochlorine pesticides	OCPs (8)	1.4; 95% CI (1.02, 1.92)		Positive	30.03	
		Phthalate esters	PAEs (6)	1.27; 95% CI (1.00, 1.60)		Positive	25.61	
		Overall	**Overall**	**1.41; 95% CI (1.23, 1.60)**		**Positive**	**100**	

Reviews

Reference	Epidemiological studies (*N*)	EDC types	EDC analysed (*N* studies)	Sample	Association	Weight (%)	Level of evidence
Smarr *et al.* (2016)	28	(A) Persistent	Metals (3)	Blood (3); Urine (1)	Positive (2); Negative (1)		**Moderate**
			Dioxins (TCDD, PCDD, PCDFs) (5)	Plasma (1); Serum (4)	Positive (2)		
			OCPs (4)	Serum (4); Fat (1)	Positive (3)		
			PBDEs (1)	Serum & Fat	Negative (1)		
			PCBs (8)	Serum (7); Plasma (1); Fat (1)	Positive (3); Negative (1)		
			PFFAs (1)	Serum (1)	Positive (1)		
		(B) Non-persistent	Benzophenone-type UV filters (1)	Urine	Positive (1)		
			BPA (1)		NS (1)		
			Phthalates (4)		Positive (2); Negative (1)		
			Overall		**14 Positive from 28**		
Guo *et al.* (2009)	17	Dioxins Dioxin-like	PCDDs PCDFs PCBs	Serum	Positive (6) NS (11)	33/100	**Moderate**

Expert Panel Analysis (European Union)

Reference	Epidemiological studies (N)	EDC types	EDC analysed (N)	Sample	Association	Weight (%)	Level of Evidence
Hunt *et al.* (2016)	DEMOCOPHES (Demonstration of a Study to Coordinate & Perform Human Biomonitoring on a European Scale) Buck Louis *et al.* (2013)	Phthalates	Σ-DEHP metabolites MEP MiBP MBP MBzP	Urine		Causation assigned probability 20–39%.	Epidemiological: **Low** Toxicological: **Moderate**

BPA: bisphenol A; DEHP: di-(2-ethylhexyl) phthalate; EDCs: endocrine-disrupting chemicals; MBP: monobutyl phthalate; MBzP: monobenzyl phthalate; MEP: monoethyl phthalate; MiBP: mono-iso-butyl phthalate; PAEs: phthalate esters; PBBs: polybrominated biphenyls; PBDEs: polybrominated diphenyl ethers; PCBs: polychlorinated biphenyls; PCDDs: polychlorinated dibenzo-p-dioxins; PCDFs: polychlorinated dibenzofurans; PFAAs: polyfluoroalkyl substances; OCPs: organochlorine pesticides; TCDD: 2,3,7,8-tetra-chlorodibenzo-p-dioxin.
NS: not significant.

Table II Association between AGD and endometriosis risk.

Reference	Study	Pathology	N (cases)	AGD_{AF}	AGD_{AC}	Odds ratio	Level of evidence
Mendiola et al. (2016)	CC (hospital)	Endometriomas	82	Significantly decreased	NS	3.5; 95% CI (1.3, 9.4), P-value = 0.04. Women in the lowest tertile of the AGD_{AF} distribution, compared w/ the upper tertile, were 3.5 times more likely to have endometriosis.	Insufficient
		DIE	32	Significantly decreased	NS	41.6; 95% CI (3.9, 438), *P* value = 0.002. Women w/ AGD_{AF} below the median, compared w/ those w/ AGD_{AF} above the median, were 41.6 times more likely to have endometriosis.	
		Endometriosis	114	Significantly decreased	NS	7.6; 95% CI (2.8, 21.0), *P* trend <0.001. Women in the lowest tertile of the AGD_{AF} distribution, compared w/ the upper tertile, were 7.6 times (95% CI 2.8, 21.0), *P* trend <0.001) more likely to have endometriosis.	
		None (control)	105				
Sanchez-Ferrer et al. (2018)	CC (hospital)	Endometriosis Endometriomas	57 45	Significantly decreased Significantly decreased	NS NS	3.72; 95% CI (1.64, 8.5), *P* value = 0.002. (22.8 ± 4.6 vs. 27.2 ± 5.7 mm), *P* trend <0.001. 2.82; 95% CI (1.23, 6.64), *P* value = 0.020	Insufficient
		Endometriosis + AMH ≤1 ng/mL	25	Significantly decreased	NS	17.4; 95% CI (5.64, 53.82) Lower AGD_{AF} & AMH are risk factors for endometriosis.	
		None (control)	93		NS		

AGD_{AC}: anogenital distance (anoclitoris); AGD_{AF}: anogenital distance (anofourchettal); AMH: anti-Müllerian hormone; CC: case-control; DIE: deep infiltrating endometriosis. NS: not significant.

(Hoshino *et al.*, 2005) and pesticides (Gray *et al.*, 1994; Matsuura *et al.*, 2005), among others, albeit other studies have reported null or positive association as reviewed by Schwartz *et al.* (2019). With respect to the controversial results obtained from animal studies, Rubin *et al.* (2019) reported in a study of mice exposed to BPA, controlling for various genetic and environmental variables associated with those experiments, that only when all the experimental conditions remained constant were the results obtained reproducible and stable. Moreover, it was shown that, depending on the dose and compound assayed, prenatal exposure to xenoestrogen pollutants affects the development of female reproductive tissues, disrupting oestrous cyclicity and folliculogenesis, increasing the presence of ovarian cysts, accelerating the onset of puberty and decreasing fertility-related indices and steroid hormones levels, gonadotropins and peptide hormones, among others (Zhou *et al.*, 2017a; Brehm *et al.*, 2018; Patiño-García *et al.*, 2018; Rattan *et al.*, 2018; Lite *et al.*, 2019; Repouskou *et al.*, 2019). Additionally, these and other alterations in the FGT are multigenerational and transgenerational up to the F3 and F4 generation (Zhou *et al.*, 2017b; Brehm *et al.*, 2018; Rattan *et al.*, 2018).

Regarding human studies, the influence of prenatal hormonal exposure on the female offspring AGD has been far less studied. Nevertheless, it was reported that hyperandrogenic conditions in pregnant women act upon the development of the reproductive system of female offspring, inducing a longer AGD at birth (Callegari *et al.*, 1987; Thankamony *et al.*, 2016) and, more recently, that newborn girls of mothers with polycystic ovary syndrome (PCOS) have a longer AGD, which suggest an elevated exposure to intrauterine testosterone (Barrett *et al.*, 2018). Along the same lines of evidence, a longer AGD in adult women has been linked to a higher content of serum testosterone (Mendiola *et al.*, 2012; Mira-Escolano *et al.*, 2014; Wu, Zhong, *et al.*, 2017). Consequently, the AGD has been identified as an endpoint in the guidelines of the US Environmental Protection Agency for reproductive toxicity studies (Liu *et al.*, 2014). However, the molecular mechanisms responsible for the development of a shorter AGD in females have not been clarified, although it could intuitively be related to a high prenatal oestrogen or anti-androgen exposure.

Therefore, recent cohort studies of pregnant mother–child pairs have analysed the AGD as a biomarker of the hormonal and EDC prenatal environment, although a definitive proof of cause–effect relationships cannot be established from these type of cohorts and only a few of them have examined prenatal EDC exposure and the AGD in female infants (Table III). Hence, as expected, these limited data showed inconsistent and sometimes non-replicable results (Arbuckle *et al.*, 2019). Thus, the meta-analysis of phthalates by Zarean *et al.* (2019) reported a non-significant association between phthalates and the female AGD; Huang *et al.* (2009) found an inverse association between monobutyl phthalate (MBP) in amniotic fluid and a shorter anogenital index adjusted by birth weight; and Arbuckle *et al.* (2018) reported a negative association of the anoclitoris distance (AGD_{AC}) and monobenzyl phthalate (MBzP), but a positive association with mono-ethyl phthalate (MEP). Regarding the effect of prenatal exposure to BPA, only Barrett *et al.* (2017) described a shorter AGD_{AC}, but there were no differences in the AGD_{AF}, while two other studies found no significant associations (Arbuckle *et al.*, 2018; Sun *et al.*, 2018). Studies of polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) in girls showed contradictory results. Torres-Sanchez *et al.* (2008) and García-Villarino *et al.* (2018) found no association

between the AGD and maternal serum levels of two polybrominated diphenyl ethers (PBDEs) and several organochlorine compounds, but the sample size was very small (only 34 and 14 girls, respectively). Loreto-Gómez *et al.* (2018) found an inverse association with the female AGD_{AF}/H index and PCB 170, but it was positive with o,p′-DDT and the mixture of o,p′-DDT and p,p′-DEE from six PCBs and several OCPs (DDT) analysed. Bornman *et al.* (2016) found no association with the level of p,p′-DDT/—DDE or o,p′-DDT, in mothers' serum, and the AGD_{AF} at delivery and after one year, while o,p′-DDE was negatively associated with the AGD_{AF} in 1-year-old girls. On the other hand, Vafeiadi *et al.* (2013) found no association between dioxin and dioxin-like compounds and decreased AGD. In turn, two studies described a null effect of triclosan (Lassen *et al.*, 2016; Arbuckle *et al.*, 2018). Finally, Dalsager *et al.* (2018) found no significant changes in the AGD, at 3 months of age, with urine levels of organophosphate and pyrethroid insecticides and the herbicide 2,4-dichlorophenoxyacetic acid at 28 weeks of pregnancy. Hence, to date, there are limited data and, thus, insufficient evidence to indicate that prenatal EDC exposure shortens the AGD in girls. Therefore, more studies are needed to include a greater number of people and to integrate their results with the experimental outcomes in animals for a given mixture of EDCs to assess the association between prenatal EDC exposure and a shorter AGD in females (Bornehag *et al.*, 2019).

The small number of studies and lack of accurate exposure measurements are the principal limitations (Zarean *et al.*, 2019). Furthermore, inconsistencies in the specific literature can be caused by multiple uncontrolled variables and methodological gaps associated with these compounds and human cohorts, including the age at which the AGD is measured and training of the staff who measure it. Additionally, most studies collected maternal EDC samples either from urine or blood at a unique and variable time point. In this regard, a recent prospective cohort study suggested that AGD in humans, as in animals, is fixed in early gestation (probably during the hypothetical masculinisation programming window, between 8 and 14 weeks) (Jain *et al.*, 2018). Hence, the EDC concentrations determined beyond those dates will be useless for the AGD outcomes. Additionally, some of the most frequently studied compounds (i.e. phthalates and BPA) are rapidly metabolized; therefore, the measurement of a single time point does not reflect the actual dose and duration of prenatal exposure. In turn, it is known that the shape of dose-response curves for endocrine compounds are often non-monotonic (Xu *et al.*, 2017), implying that it is possible that low-dose exposure to a specific EDC, such as BPA (Rubin *et al.*, 2019) or DEHP (Do *et al.*, 2012), produces phenotypic changes, while higher doses do not produce those effects. Furthermore, it has been shown that some neonatal outcomes are associated differently with prenatal exposure to individual EDC and EDC mixtures (Kelley *et al.*, 2019). In this regard, to our knowledge, no human study has focused on prenatal exposure to defined mixtures of EDC and AGD. On the other hand, differences between individuals and inter-race in human studies are a common issue that produces great heterogeneity of the recorded data (Wenzel *et al.*, 2018), preventing significant conclusions from studies carried out using a small sample size.

Nevertheless, despite the inconsistent results, there is growing experimental and epidemiological evidence and concern about the effects of environmental or synthetic EDCs on alterations of normal immune cell development (Kelley *et al.*, 2019; Nowak *et al.*, 2019), FGT reproductive function (Crain *et al.*, 2008; Patel *et al.*, 2015; Leonardi *et al.*, 2017; Rashtian *et al.*, 2019) and several gynaecologic diseases (Gore *et al.*, 2015; Paulose *et al.*, 2015; Hunt *et al.*, 2016; Smarr *et al.*, 2016; Piazza and Urbanetz, 2019; Wen *et al.*, 2019). Concretely, a recent longitudinal study with pregnant mothers and their children until 9–13 years has revealed that prenatal exposure to phthalates, parabens and phenols during the *in utero* windows of susceptibility is associated with earlier puberty in girls (Harley *et al.*, 2019), although inconsistent results have also been described as reviewed by Lee *et al.* (2019).

According to these observations, it is tempting to speculate that a high level of exposure to EDCs or other still unknown compounds during prenatal life could not only modify the AGD and induce earlier menarche (considered a risk factor for endometriosis) (Nnoaham *et al.*, 2012; Parasar *et al.*, 2017; Parazzini *et al.*, 2017; Shafrir *et al.*, 2018) but also alter other sexual features, such as the normal development of uterine endometrial tissue or the length and morphology of the uterus and fallopian tubes, which could be risk factors for the development and further progression of endometriosis. In this regard, studies in DES-daughter cohorts have revealed several morphologic and functional alterations of the FGT (Swan, 2000; Reed and Fenton, 2013) and Missmer *et al.* (2004) found a higher risk of endometriosis among women prenatally exposed to DES.

Therefore, based on those reported observations, we posit a direct relationship between higher prenatal exposure to oestrogens, anti-androgenic EDCs or other undetermined factors, a shorter AGD and a higher risk of developing endometriosis after menarche.

Human Female Genital Tract Microbiome

Another risk factor increasingly implicated in the aetiology and pathogenesis of endometriosis is the composition of gut microbiota and its corresponding metabolic activity (Kobayashi *et al.*, 2014; Laschke and Menger, 2016; Khan *et al.*, 2018). As mentioned above, there is an evident and close relationship between a healthy gut microbiota and correct development and function of the immune system (Smolinska and O'Mahony, 2016; Levy *et al.*, 2017; Pabst, 2017). In fact, the acquisition and maintenance of a suitable microbiota in early life seem to be a determining factor in maintaining a healthy state throughout life (Houghteling and Walker, 2015; Stinson *et al.*, 2017). In this sense, the degradation of certain glycans and mucin by commensal bacteria can act as a means of communication between the microbiota and host. Among them, short-chain fatty acids (SCFA) such as acetate, butyrate and propionate, produced from carbohydrate metabolism, can diffuse through the mucus layer, reach the surface of epithelial cells and exert important biological functions (Corrêa-Oliveira *et al.*, 2016; Morrison and Preston, 2016).

Alteration of the composition and functionality of microbial populations is known as dysbiosis, which is being increasingly linked to the susceptibility and aggravation of several diseases (Thomas *et al.*, 2017), including obesity (Riva *et al.*, 2017), metabolic syndrome (Festi *et al.*, 2014), chronic inflammatory diseases (gluten intolerance, inflammatory bowel disease) (Buttó and Haller, 2016), immune disorders (Levy *et al.*, 2017; Felix *et al.*, 2018) and even autism and depression (Rieder *et al.*, 2017), although it remains unknown whether dysbiosis is itself a cause or a consequence of these pathologies.

Table III Association between EDCs and female AGD.

EDC	Reference	Cohort (country)	Epidemiological study	*N* (mothers/girls)	EDC analysed (*N*)	Maternal sample	AGD_{AF} odds ratio†	AGD_{AF} association	AGD_{AC} odds ratio†	AGD_{AC} association	AGD_{AF} results significance	AGD_{AF} weight EDCs	Level of evidence
Phthalates	Swan *et al.* (2015)	TIDES (USA)	Mother/infant cohort	758/387	Phthalates (11): MEP, MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, MCOP, MCNP, MCPP	Urine (1st trimester)	2 negative & 9 positive (NS)	11 (NS)	5 negative, 5 positive & 1 unchanged (NS)	11 (NS)	**NS**		
	Adibi *et al.* (2015)	TIDES (USA)	Mother/infant cohort	541/275	Phthalates (8): MnBP, MBzP, MEHP, MEP, MiBP, MCPP, MCNP, MCOP	Urine (1st trimester)	MnBP: $\beta = 0.30$; 95% CI (0.09, 0.51), $P < 0.01$ MBzP: $\beta = 0.21$; 95% CI (0.03, 0.39), $P = 0.2$ MEHP: $\beta = 0.34$; 95% CI (0.13, 0.55), $P < 0.01$	3 larger (S), 1 shorter (NS) & 4 larger (NS) from 8	ND	ND	**3 significantly increased from 8**		
	Barrett *et al.* (2016)	TIDES (USA)	Mother/infant cohort	738/372	Phthalates (9): MEHP, ΣDEHP, MEP, MnBP, MBzP, MEHHP, MEOHP, MECPP, MiBP, MCPP	Urine (1st trimester)	2 negative, 6 positive & 1 null from 9 (NS)	2 shorter (NS), 6 larger (NS) & 1 unchanged from 9	3 positive & 6 negative (NS)	9 (NS)	**NS**	**4 significantly larger & 1 significantly shorter from 13 assayed**	**Insufficient**

Continued

Table III *Continued.*

EDC	Reference	Cohort (country)	Epidemio-logical study	*N* (mothers/ girls)	EDC analysed (*N*)	Maternal sample	AGD_{AF} odds ratio†	AGD_{AF} association	AGD_{AC} odds ratio†	AGD_{AC} association	AGD_{AF} results significance	AGD_{AF} weight EDCs	Level of evidence
Phthalates	Wenzel *et al.* (2018)	(USA)	Mother/ infant cohort	380 (187 African American & 193 white)/ 128	Phthalates (8): MBP, MiBP, MBzP, MEOHP, MEHP, MEHHP, MEP, MMP	Urine (2nd trimester)	MiBP: $\beta = 0.72$; 95% CI (0.09, 1.35), $P = 0.03$ 4 negative 3 positive (NS)	1 larger (S), 4 shorter (NS) & 3 larger (NS) from 8	All women: 5 negative & 3 positive (NS). Significant race-based interaction: AGD was longer for whites & shorter for African. MEP: $\beta = -1.13$ 95% CI (−1.90, −0.35), $P = 0.01$ ΣDBP: $\beta = -0.77$; 95% CI (−2.06, 0.51), $P = 0.08$.	5 shorter (NS) & 3 larger (NS) from 8. 2 (S) shorter in African American. Significant race-based interaction	**1 significantly increased from 8.**		
	Zarean *et al.* (2019)	**Meta-analysis***	4 (mother/ infant) cohorts		Phthalates (10)	Urine	MBzP: $\beta = 0.178$; 95% CI (0.045, 0.311)	1 larger (S) from 10	No association	No association	**Overall: NS**		
	Huang *et al.* (2009)	Taiwan	Mother/ infant cohort	83/31	Phthalates (5): MBP, MEHP MEP, MBzP, MMP	Urine & amniotic liquid	Significant inverse association between amniotic fluid MPB & AGD: $\beta = -0.31$, $P < 0.06$ AGD index adjusted by birth weight (AGI-W): $\beta = -0.32$, $P < 0.05$ AGD index adjusted by birth length (AGI-L) $\beta = -0.33$, $P < 0.05$	1 shorter (S), 3 shorter (NS) & 1 larger (NS) from 5	ND	ND	**1 significantly decreased from 5**		

Continued

Table III *Continued.*

EDC	Reference	Cohort (country)	Epidemio-logical study	*N* (mothers/ girls)	EDC analysed (*N*)	Maternal sample	AGD_{AF} odds ratio†	AGD_{AF} association	AGD_{AC} odds ratio†	AGD_{AC} association	AGD_{AF} results significance	AGD_{AF} weight EDCs	Level of evidence
Phthalates	Arbuckle *et al.*, 2018	Canada (MIREC)	Mother/ infant cohort	396/195 at birth	Phthalates (11): MEP, MnBP, MBzP, MNHHP, MCPP, MEOHP, MEHP, ΣDEHP, ΣLMW, ΣHMW, ΣMC	Urine (1st trimester)	4 negative & 7 positive (NS)	11 (NS)	MBzP: $\beta = -1.24$; 95% CI (−1.91, −0.57), $P = 0.0004$ MEP: $\beta = 0.65$; 95% CI (0.12, 0.18), $P = 0.02$; 1 larger & 8 shorter (NS)	1 shorter (S), 1 larger (S), 8 shorter (NS) & 1 larger (NS) from 11	**NS**		
BPA	Arbuckle *et al.*, 2018	Canada (MIREC)	Mother/ infant cohort	396/195 at birth	BPA	Urine (1st trimester)	Positive (NS)	Larger (NS)	Negative (NS)	Shorter (NS)	**NS**		
	Sun *et al.*, 2018	China (Shanghai-Minhang Birth Cohort Study)	Mother/ Infant Cohort	982/infants	BPA	Urine samples collected at 12–16 gestational weeks. AGD at birth, at 6 & 12 months	At birth & 6 months age positive (NS) at 12 months negative (NS)	Larger (NS) at birth & 6 months age shorter at 12 months (NS)	At birth & 12 months age negative (NS) at 6 months positive (NS)	Larger at 6 months age (NS). Shorter at birth & 12 months age (NS).	**NS**	**NS effect**	**Insufficient**
	Barrett *et al.*, 2017	USA (TIDES)	Mother/ Infant Cohort	385/380	BPA	Urine (1st trimester)	Positive (NS)	Larger (NS)	Log (fSpG-adj BPA) vs. AGD_{AC}: $\beta = -0.56$; 95% CI (−0.97, −0.15), $P < 0.05$	Shorter (S)	**1 AGD_{AC} significantly decreased**		

Continued

Table III *Continued.*

EDC	Reference	Cohort (country)	Epidemio-logical study	*N* (mothers/ girls)	EDC analysed (*N*)	Maternal sample	AGD_{AF} odds ratio†	AGD_{AF} association	AGD_{AC} odds ratio†	AGD_{AC} association	AGD_{AF} results significance	AGD_{AF} weight EDCs	Level of evidence
OCs	Torres-Sanchez *et al.* (2008)	Mexico	Cross-sectional. Part of an ongoing perinatal cohort	382/34 (3–18 months age)	DDT metabolites (p,p′-DDE & p,p′-DDT)	Maternal serum levels before & during each trimester of pregnancy	NS changes	Null effect	ND	ND	**No effect**	**NS effect**	**Insufficient**
	Loreto-Gomez *et al.* (2018)	Mexico	Mother/ infant cohort	156/84 (1st year)	PCBs: 28, 74, 118, 138/158, 153, 170, 180 DDT isomers (o,p'-DDT, p,p'-DDT) p,p'-DDE	Mother blood (3rd trimester of pregnancy)	o,p′-DDT: $\beta = 0.0001$; 95%CI (0.00003, 0.00026), $P = 0.008$ PCB 170: $\beta = -0.0007$; 95%CI (−0.0015, 0.00001), $P = 0.05$. The mixture of o,p′-DDT & p,p′-DDE: C1: $\beta = 0.0005$; 95% CI (0.0001, 0.001), $P = 0.013$. C2: $\beta = 0.0008$; 95% CI (0.0001, 0.001), $P = 0.017$	3 larger (S), 1 shorter (S) from 10	5 negative, 4 positive & 1 unchanged (NS)	5 shorter (NS) & 4 larger (NS)	**3 increased & 1 decreased significantly from 10**		
	García-Villarino *et al.* (2018)	Spain (INMA)	Mother child cohort	355/14 (18th months)	HCB 2, 4-DDD 4,4-DDD PCBs (4) PBDEs	Mother blood (1st trimester)	NS changes	3 shorter (NS), 5 larger (NS) from 8	ND	ND	**NS**		
	Bormann *et al.* (2016)	South Africa (VHEMBE)	Longitudinal birth cohort study	752/327 (at birth) & 324 (age 1 year)	p,p′-(DDT & DDE) o,p′-(DDT & DDE)	Mother blood samples at delivery	At birth: 2 positive & 2 negative (NS). 1 year: o,p′-DDE: $\beta = -1.32$ (−2.27, −0.38) $P < 0,05$ (S) & 3 negative (NS).	At birth: 2 shorter (NS) 2 larger (NS) from 4. At 1 year age: 1 shorter (S) 3 shorter (NS) from 4.	At birth: 2 positive (NS) & 2 null. At 1year age: 2 positive & 2 negative (NS).	At birth: 2 larger (NS) & 2 unchanged. At 1 year age: 2 shorter (NS) & 2 larger (NS).	**At birth NS. At 1 year: 1 significantly decreased**		

Continued

Table III *Continued.*

EDC	Reference	Cohort (country)	Epidemio-logical study	*N* (mothers/ girls)	EDC analysed (*N*)	Maternal sample	AGD_{AF} odds ratio†	AGD_{AF} association	AGD_{AC} odds ratio†	AGD_{AC} association	AGD_{AF} results significance	AGD_{AF} weight EDCs	Level of evidence
OCs	Vafeiadi *et al.* (2013)	Spain-Greece ('Rhea')	Mother/child cohort	205/109 newborn & 219 young girls	Dioxin-like compounds (DR CALUX® bioassay)	Plasma dioxin-like activity in maternal blood samples at delivery	At birth: negative (NS) Young girls: positive (NS)	At birth: shorter (NS). Young girls: larger (NS).	At birth: positive (NS). Young girls: positive (NS).	At birth: larger (NS). Young girls: larger (NS).	**NS**		
Triclosan	Arbuckle *et al.* (2018)	Canada (MIREC)	Mother/ infant cohort	396/195 (at birth)	TCS	Urine (1st trimester)	Negative (NS)	Shorter (NS)	Positive (NS)	Larger (NS)	**NS**	**NS effect**	**Insufficient**
	Lassen *et al.* (2016)	Denmark (Odense Child Cohort)	Mother–child cohort	514/178 (AGD_{AF}) & 176 (AGD_{AC}) at 3 months age	TCS	Urine samples at approx. gestation week 28 (median 28.7 weeks)	Negative (NS)	Shorter (NS)	Negative (NS)	Shorter (NS)	**NS**		
Pesticides	Dalsager *et al.* (2018)	Denmark (Odense Child Cohort)	Mother–child cohort	850/326	**Pesticide metabolites:** 3-PBA TCPY DAPs 2,4-D	Urine in gestation week 28	2,4-D: Positive (NS) 3BPA: Positive (NS) TCPY: Positive (NS) DAPs: 2 Positive (NS) & 1 Null	2,4-D: Larger (NS) 3BPA: Larger (NS) TCPY: Larger (NS) DAPs: 2 Larger (NS), 1 unchanged	2,4-D: Negative (NS) 3BPA: Positive (NS) TCPY: Positive (NS) DAPs: 3 Positives (NS)	2,4-D: Shorter (NS) 3BPA: Larger (NS) TCPY: Larger (NS) DAPs: 2 Larger (NS)	**NS**	**NS effect**	**Insufficient**

2,4-D: 2,4-dichlorophenoxyacetic acid; 2,4-DDD: 2,4-dichlorodiphenyldichloroethane; 3-PBA: 3-phenoxybenzoic acid; 4,4-DDD: 1,1-dichloro-2,2–bis(4-chlorophenyl)ethane; AGD_{AC}: anogenital distance (anoclitoris); AGD_{AF}: anogenital distance (anofourchettal); AGI: anogenital index; BBzP: butylbenzyl phthalate; BPA: bisphenol A; DAPs: dialkyl phosphates; DBP: dibutyl phthalate; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; DEHP: di-(2-ethylhexyl) phthalate; DEP: diethyl phthalate; DIBP: di-isobutyl phthalate; DIDP: di-isodecyl phthalate; DINP: di-isononyl phthalate; DMP: dimethyl phthalate; DnBP: di-n-butyl phthalate; DnOP: di-n-octyl phthalate; EDCs: endocrine-disrupting chemicals; HCB: hexachlorobenzene; MBP: monobutyl phthalate; MBzP: monobenzyl phthalate; MCHP: mono-cyclohexyl phthalate; MCNP: mono-carboxy-isononyl phthalate; MCOP: mono-carboxy-isooctyl phthalate; MCPP: mono-3-carboxy-propyl phthalate; MECPP: mono-2-ethyl-5-carboxypentyl phthalate; MEHHP: mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP: mono-2-ethylhexyl phthalate; MEOHP: mono-2-ethyl-5-oxohexyl phthalate; MEP: monoethyl phthalate; MiBP: mono-iso-butyl phthalate; MiNP: mono-isononyl phthalate; MMP: monomethyl phthalate; MnBP: mono-n-butyl phthalate; MnOP: mono-n-octyl phthalate; NS: no significant; OCs: organochlorines; OCPs: organochlorine pesticides; o,p′-DDT: o,p′-dichlorodiphenyltrichloroethane; PAEs: phthalate esters; PBBs: polybrominated biphenyls; PBDEs: polybrominated diphenyl ethers; PCBs: polychlorinated biphenyls; PCB 28: 2,4,4′-trichlorobiphenyl; PCB 74: 2,4,4′,5-tetrachlorobiphenyl; PCB 118: 2,3′,4,4′,5-pentachlorobiphenyl; PCB 138: 2,2′,3,4,4′,5′-hexachlorobiphenyl; PCB 153: 2,2′,4,4′,5,5′-hexachlorobiphenyl; PCB 170: 2,2′,3,3′,4,4′,5-heptachlorobiphenyl; PCB 180: 2,2′,3,4,4′,5,5′-heptachlorobiphenyl; PCDDs: polychlorinated dibenzo-p-dioxins; PCDFs: polychlorinated dibenzofurans; PFAAs: polyfluoroalkyl substances; p,p′-DDE: p,p-dichlorodiphenyldichloroethylene; p,p'-DDT: p,p′-dichlorodiphenyltrichloroethane; TCDD: 2,3,7,8-tetra-chlorodibenzo-p-dioxin; TCPY: 3,5,6-trichloro-2-pyridinol; TCS: triclosan; ΣDEHP: molar sum of di-(2-ethylhexyl) phthalate metabolites; ΣHMW: molar sum of high molecular weight phthalate metabolites; ΣLMW: molar sum of low molecular weight phthalate metabolites; ΣMC: molar sum of medium-chain phthalate metabolites; ND: not determined; NS: not significant

†Odds ratios indicated only for significant associations.

*Meta-analysis from the four original studies shown above.

Microbiome colonisation of the FGT could have a different origin following distinct routes, as suggested by data on prenatal colonisation (Collado *et al.*, 2016; Stinson *et al.*, 2017; Peric *et al.*, 2019) (Fig. 2).

The first source may be the intestinal microbiota after crossing the bowel wall by a process mediated by DCs present in the lamina propria (Macpherson and Uhr, 2004). These cells could actively penetrate the intestinal epithelium, capture commensal bacteria from the lumen and transport them to the mesenteric lymph nodes and then through the lymphatic system to the blood (Rescigno *et al.*, 2001; Smolinska and O'Mahony, 2016; Stinson *et al.*, 2017). However, it is possible that this transport is also carried out directly through the bloodstream (Païssé *et al.*, 2016; Castillo *et al.*, 2019).

A second source of upper FGT bacteria would be the vulva and vagina, from which certain bacterial species would ascend (Baker *et al.*, 2018).

The third possible source of bacteria would be the oral cavity, from which they could be transported by the bloodstream to the FGT (Aagaard *et al.*, 2014; Baker *et al.*, 2018) (Fig. 2). In this sense, it was described that the placental and maternal oral microbiota are very similar (Aagaard *et al.*, 2014; Gomez-Arango *et al.*, 2017), sharing genera such as *Prevotella* and *Neisseria* (Aagaard *et al.*, 2014). Additionally, numerous studies have linked the presence of pathogenic bacteria (*Fusobacterium nucleatum*, *Porphyromonas gingivalis*) that cause periodontal diseases, such as gingivitis or periodontitis, with preterm birth because these bacteria were detected in the mouth, placenta and amniotic fluid of affected women (León *et al.*, 2007; Han, 2015). This suggests that oral bacteria can migrate at a distance both under physiological conditions and in periodontal disease.

Cervicovaginal Microbiota

The urogenital microbiota accounts for only ~9% of the total, containing 10^8 UFC per gram of vaginal mucus (Delaney and Onderdonk, 2001; Smith and Ravel, 2017). Moreover, while the gut microbiota is highly diverse, the vaginal microbiome usually displays low diversity within each individual, with a preponderance of *Lactobacillus* species in most white premenopausal women (Zhou *et al.*, 2007; Ravel *et al.*, 2011; Human Microbiome Project Consortium, 2012; Drell *et al.*, 2013; Chaban *et al.*, 2014; Koedooder *et al.*, 2019). *Lactobacilli* communities are considered the most beneficial components in the vagina of reproductive-age women (Turnbaugh *et al.*, 2007; NIH HMP Working Group *et al.*, 2009; Ma *et al.*, 2012; Aagaard *et al.*, 2013). In this regard, 16S rRNA gene amplicon sequencing studies identified five groups of vaginal microbiota, among which three or four contain more than 90% of *Lactobacillus* (Ravel *et al.*, 2011; Gajer *et al.*, 2012; Ding and Schloss, 2014). The most abundant species are *L. crispatus*, *L. iners*, *L. jensenii* and *L. gasseri* (Burton and Reid, 2002; Pavlova *et al.*, 2002; Vásquez *et al.*, 2002; Thies *et al.*, 2007; Vitali *et al.*, 2007; Shi *et al.*, 2009; Yamamoto *et al.*, 2009; Zhou *et al.*, 2007; Hyman *et al.*, 2012). Nevertheless, the relative proportions of *Lactobacillus* and their species differ among ethnic groups and territorial locations (Pavlova *et al.*, 2002). *Lactobacillus* species of vaginal microbiota generate lactic acid from carbohydrate metabolism sustaining a low pH (between 3.5 and 4.5), hydrogen peroxide and bacteriocins, inhibiting the growth of pathogens and contributing to maintenance of local homeostasis (Aroutcheva *et al.*, 2001; Ghartey *et al.*, 2014). However, *Lactobacillus* species differ in their beneficial effects. *Lactobacillus crispatus* has been associated with a healthy vaginal environment, while *L. iners* seems to be less protective against colonisation by pathogenic microbial species. A study of African women (Jespers *et al.*, 2017) has concluded that a higher 'composite-qPCR vaginal-health-score' was associated with decreased concentrations of pro-inflammatory cytokines (IL-1α, IL-8, IL-12p70) and an increased level of the chemokine IP-10 (CXCL10), compatible with homeostasis.

Dysbiosis of the Female Genital Microbiome

Vaginal dysbiosis produces significant changes in this scenario (Fig. 3D) and is frequently associated with an increased risk of getting *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis* and human immunodeficiency virus (HIV) (Atashili *et al.*, 2008; Brotman *et al.*, 2010).

In this regard, the CV microbiota in a cohort of HIV-negative asymptomatic young South African women (Anahtar *et al.*, 2015) showed four cervicotypes (CT): CT1 with a dominance of *L. crispatus* and the absence of *L. iners*, *Gardnerella* and *Prevotella*; CT2 where *L. iners* was dominant; CT3 with a predominance of *Gardnerella*; and CT4 with higher bacterial diversity, but usually including *Prevotella*. Although only a minority of women had a *Lactobacillus*-dominant CV microbiota, a strong relationship was found between a highly diverse vaginal microbiota, low in *Lactobacillus* (CT4 and in a less prominent way, CT3) and a higher level of several pro-inflammatory cytokines (IL-1α, IL-1β, TNF-α, IFN-γ, IL-8, IL-12p70 and FLT-3L). Likely, vaginal and endocervical lipopolysaccharide (LPS) could be detected by TLR-4 expressed on APCs, secreting a wide variety of pro-inflammatory cytokines and T-cell chemokines (as reviewed previously by Hickey *et al.*, 2011). These results strongly suggest that specific members of genital bacteria could elicit a strong local immune response but also demonstrate that CV dysbiosis can coexist with an asymptomatic or subclinical FGT scenario.

Bacterial vaginosis (BV), the most common type of vaginal dysbiosis, is generally characterised by the replacement of *Lactobacilli* by anaerobic species such as *Gardnerella* and *Mobiluncus* genera. Sialidases produced by several bacteria such as *Gardnerella* and *Prevotella*, as well as IgA proteases, evade recognition by antibodies; SCFAs enhance bacterial adherence to epithelial cells and can regulate the mucosal immune response (Onderdonk *et al.*, 2016).

Several recent works have described that specific members (*Prevotella amnii*, *Mobiluncus mulieris*, *Sneathia amnii* and *Sneathia sanguinegens*) within the highly diverse CV microbiota induce high levels of the pro-inflammatory cytokines IL-1α, IL-1β and IL-8 and chemokines by vaginal APCs and epithelial cells, which recruit cells of the adaptive immune system, mainly CD4+ T cells in infected tissue (Anahtar *et al.*, 2015). In the same line of evidence, women from India presenting infertility problems had a lower percentage of vaginal *Lactobacillus* species, a higher prevalence of asymptomatic vaginosis and an abundance of vaginosis-associated bacteria compared with healthy women (Babu *et al.*, 2017). Additionally, women with BV episodes had significantly lower concentrations of *Lactobacilli* and higher concentrations of *G. vaginalis*, *Atopobium vaginae* and *Prevotella bivia*, which are associated

with increased vaginal concentrations of pro-inflammatory cytokines (IL-1β, IL-12p70) and decreased levels of IP-10 and elafin (an epithelial proteinase inhibitor) (Jespers et al., 2017). Campisciano et al. (2018) described that women with overt BV presented a massive increase in non-resident vaginal species and a low presence of *G. vaginalis*. Vaginal dysbiosis induced a simultaneous increase in the pro-inflammatory T_H1 cytokine IL-2 and anti-inflammatory IL-1ra and a decrease in FGF-β and GM-CSF growth factors. Moreover, the grade of vaginal dysbiosis was associated with a specific pattern of mediators, including IL-1α, IL-1β, IL-8, MIG, MIP-1α and RANTES. Notably, an increase in anti-inflammatory IL-5 and IL-13 paralleled the depletion of *Lactobacilli* ssp., *G. vaginalis* and *Ureaplasma* spp., suggesting a role for the activation of the CD4+ T_H2 subset in counteracting the T_H1 response and its corresponding clinical symptoms, which could explain the high frequency of asymptomatic BV.

In conclusion, as reviewed by Anahtar et al. (2018), resident bacterial communities of a healthy lower FGT are dominated by *Lactobacilli*, especially by its beneficial member *Lactobacillus crispatus* (Ghartey et al., 2014), which is directly related to a low inflammatory CV environment. Conversely, dysbiosis of the CV microbiota can begin a gradual array of FGT immune dysfunctions from asymptomatic to subclinical and overt BV, which, in turn, could be the origin of several obstetrical, gynaecological and urogenital pathologies, such as BV, sexually transmitted diseases, urinary infections and preterm birth (Ma et al., 2012; Hyman et al., 2014; Anahtar et al., 2018).

Upper Genital Tract Microbiota

Although the vagina harbours a significant amount of bacteria, the upper genital tract has been largely considered a sterile area. The endocervix acts as a physical–chemical immune barrier because it is plugged by a thick layer of mucus that contains antibodies (IgG and secretory IgA), antimicrobial proteins and antimicrobial peptides, including lysozyme, lactoferrin, defensins, cathelicidins, calprotectin, trappin-elafin and likely others (Valenti et al., 2018). Its main component, mucin, varies its conformation throughout the menstrual cycle, depending mainly on pH variations (Brunelli et al., 2007), which could allow bacteria to enter the uterus under some situations. In fact, the analysis of bacterial cultures from hysterectomy samples performed in the 1990s revealed the growth of microorganisms from the uterus, among which the most frequently identified were *Lactobacillus* species, *Mycoplasma hominis*, *Gardnerella vaginalis* and *Enterobacter* (Cowling et al., 1992; Møller et al., 1995).

Recently, Chen et al. (2017) systematically sampled the microbiota in six FGT locations in 110 Chinese women of reproductive age by 16S rRNA gene amplicon sequencing and bacterial culture. Their results revealed the presence of a microbiota continuum along the FGT, with different profiles within each woman. Hence, distinct bacteria were identified in the vagina, cervical canal, uterus, fallopian tubes and peritoneal fluid. According to previous work from different countries, the microbiota of the lower third of the vagina and posterior fornix were mostly integrated with *L. crispatus*, *L. iners* and other *Lactobacillus* spp. showing low diversity (Ravel et al., 2011; Gajer et al., 2012; Ding and Schloss, 2014). The mucus of the cervical canal harboured a lower frequency of *Lactobacillus* spp. than the vaginal compartment. Endometrial samples had lower proportions of *Lactobacillus* spp., and the predominant microbiota comprised *Pseudomonas*, *Acinetobacter*, *Vagococcus* and *Sphingobium*. Furthermore, the frequency of these species was increased in the fallopian tubes, which have only 1.69% of *Lactobacillus* spp. Finally, while *Lactobacillus* spp. was absent in the peritoneal fluid, it contained a diverse microbiota, albeit not identical to that of the fallopian tubes. Regarding the *phylum* level, *Firmicutes* was predominant in the lower genital tract. In the upper tract, the dominant bacteria belonged to *Proteobacteria*, *Actinobacteria* and *Bacteroidetes*. Notably, they also identified microbial taxa and potential functions correlating with the menstrual cycle or overrepresented in women with adenomyosis or infertility due to endometriosis, suggesting that surveying the vaginal or cervical microbiota could be useful to detect common diseases affecting the upper reproductive tract. Recent reviews from Baker et al. (2018) and Koedooder et al. (2019) have summarised the current status of studies on the uterine bacterial microbiome, discussing the level at which these microorganisms are residents that maintain the homeostasis, transients to be eliminated or harmful species contributing to FGT pathologies.

Potential Role Played by Subclinical Infections of the Female Genital Tract in the Development of Endometriosis

Recent hypotheses and growing evidence have suggested an active role of genital subclinical microbial infections in the development and clinical progression of endometriosis (Table IV). Khan et al. (2010) established the 'hypothesis of bacterial contamination in endometriosis' based on their findings of high contamination levels of *Escherichia coli* and LPS in the menstrual blood of patients with endometriosis, as well as high LPS concentrations in their peritoneal fluids (Khan et al., 2012, 2018). They also described that the engagement of TLR4/LPS could regulate the growth of endometriosis (Khan et al., 2013). Using bacterial cultures, they observed a higher content of intrauterine bacteria and endometritis in women with endometriosis, which increased further after treatment with a gonadotropin-releasing hormone agonist (GnRHa) (Khan et al., 2014). More recently, by 16S rDNA metagenome sequence analysis, they found that the frequency of Lactobacillaceae significantly decreased, while the presence of Streptococcaceae, Staphylococcaceae, Enterobacteriaceae significantly increased in women with endometriosis treated with GnRHa compared with untreated women, likely contributing to further aggravating the progression of endometriotic lesions and associated symptoms. These results demonstrate the regulatory effects of sexual hormones on the FGT microbiota. Moreover, higher percentages of Streptococcaceae and Staphylococcaceae were detected in the cystic fluid obtained from patients with ovarian endometrioma than in those extracted from non-endometrioma cysts (Khan et al., 2016). Additionally, the fertility outcomes of endometritis patients significantly improved after antibiotic treatment, supporting the influence of microorganisms in this problem (Cicinelli et al., 2014). Kobayashi et al. (2014) postulated a model in which an initial bacterial challenge, likely with Gram-bacteria because of their high LPS content, followed by a sustained sterile inflammation would allow a vicious circle to be established leading to the development of endometriosis.

Table IV Association between microbiome and endometriosis.

Association studied	Reference	Study (country)	Sample size	Endometriosis diagnostic	Sample	Methods	Results	Association	Level of evidence
Endometriosis/ Bacteria	Ata *et al.* (2019)	Prospective observational (Turkey)	14 women w/ endometriosis 14 asymptomatic women (control)	Laparoscopy (histology)	Stool, vaginal & endocervical swabs	16S rRNA gene sequencing (bacteria)	Cervix, vagina & gut similar bacteria (no differences). Differences at the genus level in endometriosis patients: Absence of *Atopobium* in vagina & cervix. Increase of *Gardnerella, Streptococcus, Escherichia, Shigella*, & *Ureaplasma* in the cervix. *Shigella*/*Escherichia* dominant stool microbiome.	**Positive association but NS**	**Insufficient**
	Campos *et al.* (2018)	Cross-sectional (Brazil)	73 women w/ endometriosis 31 asymptomatic women (control)	Laparoscopy (histology)	Endocervical swabs Peritoneal fluid biopsies from lesions	PCR (bacteria) Luminex (cytokines)	No statistically significant differences were detected in the swab & peritoneal samples in *Mycoplasma hominis, M. genitalium, Ureaplasma urealyticum, & U. parvum*. *Ureaplasma parvum was* associated w/ dyspareunia. *Mycoplasma genitalium* was associated w/ increased IFN-γ, IL-1β.	**NS**	
	Khan *et al.* (2014)	Case–control (Japan)	65 women w/ endometriosis 55 control women	Laparoscopy (histology)	Vaginal smears Endometrial samples	Bacterial culture	Vaginal pH $\geq$ 4.5: 79.3% endometriosis versus 58.4% Control ($P < 0.03$). The number of (CFU/ml) of		
							Gardnerella, α-Streptococcus, Enterococci & Escherichia coli was significantly higher in endometrial samples from women w/ endometriosis than control women ($P < 0.05$ for each bacteria).	**Higher CFU/mL Significant difference**	
	Akiyama *et al.* (2019)	Case–control (Japan)	30 women w/ endometriosis (stage 3/4) 39 w/o endometriosis (w/ fibroids or benign ovarian tumour)	Laparoscopy (histology)	Cervical mucus	Bacterial DNA extraction & PCR amplification of 16S rRNA gene. Amplicon sequencing using NGS.	The amount of *Enterobacteriaceae* & *Streptococcus* was significantly higher in the cervical mucus of endometriosis group than that in the control group ($P < 0.05$). The populations of *Corynebacterium*, *Enterobacteriaceae*, *Flavobacterium, Pseudomonas*, & *Streptococcus* were increased in the endometriosis group.	**Higher significant differences**	

Continued

Table IV *Continued*

Association studied	Reference	Study (country)	Sample size	Endometriosis diagnostic	Sample	Methods	Results	Association	Level of evidence
	Tai *et al.* (2018)	Retrospective cohort (Taiwan)	28 292 women w/ pelvic inflammatory disease (PID) 113 168 w/o PID (control)	Ultrasonography or laparoscopy	Comorbilities associated to endometriosis	Database	Hazard ratio for endometriosis/PID association: $\beta = 3.02$; 95% CI (2.85, 3.2), $P < 0.0001$	**Significant association**	
Endometriosis/FGT infectious diseases	Lin *et al.* (2016)	Retrospective based cohort (Taiwan)	79 512 women w/ lower FGT inflammatory diseases & 79 512 w/o FGT inflammatory diseases.	Ultrasonography or laparoscopy	Database	Database	Hazard ratio: $\beta = 2.01$; 95% CI (1.91, 2.12), $P < 0.001$ Incidence of endometriosis was higher among inflammatory disease patients than controls.	**Significant association**	**Insufficient**
	Takebayashi *et al.* (2014)	Case–control (Japan)	34 patients w/ endometriosis. 37 w/o endometriosis. 28 w/ chronic endometritis. 43 w/o chronic endometritis.	Immunohistochemistry	Uterus from hysterectomy	Immunohistochemistry	Logistic regression analysis revealed that endometriosis was associated w/ chronic endometritis Odds ratio: 3.037; 95% CI (1.129, 8.174), $P = 0.028$	**Significant association**	
Endometriosis/ periodontal disease	Thomas *et al.* (2018)	Case–control (India)	25 women w/ endometriosis. 25 w/o endometriosis (control).	Laparocopy (histology)	Periodontal screening	Clinical examination	Gingival index was seen to be significantly higher in patients w/ endometriosis: (1.55 ± 0.53) in cases & (1.12 ± 0.25) in controls, $P = 0.001$ Proportion of women w/ moderate-to-severe periodontitis was seen to be higher among women w/ endometriosis. Severe periodontitis & endometriosis: OR: 2.9; 95% CI (0.76, 11.33), $P = 0.09$	**Positive association but NS**	**Insufficient**
	Kavoussi *et al.* (2009)	Cross-sectional (NHANES (USA))	4136 women w/ periodontal disease & endometriosis	Self-reported endometriosis	Database	Clinical oral health examination	Adjusted OR = 1.57; 95% CI (1.06, 2.3) for gingivitis plus periodontitis. Women w/ self-reported endometriosis had significantly (57%) higher odds of having both gingivitis & periodontitis.	**Significant association**	

PID: pelvic inflammatory disease; NS: not significant.

A recent study of a Taiwan cohort including a total of 79 512 patients with lower FGT inflammatory diseases revealed that the presence of endometriosis was statistically higher in patients than in control women (Lin *et al.*, 2016). The association between chronic endometritis and endometriosis has also been reported (Takebayashi *et al.*, 2014). The work of Chen *et al.* (2017) reported the presence (from the vagina up to peritoneal fluid) of *Streptococci* (45–60%), *Staphylococci* (35–87%), *Ureaplasma* (2–55%) and *Chlamydia* (0–3.2%) in women with endometriosis, agreeing with previous results obtained from endometrial cultures of women with chronic endometritis (Cicinelli *et al.*, 2008) and endometrial cancer (Walther-António *et al.*, 2016). Wang *et al.* (2018) reported the presence of *Proteobacteria* and *Firmicutes*, followed by *Actinobacteria*, *Bacteroides*, *Fusobacterium* and *Tenericutes* in the peritoneal fluid of women with and without endometriosis, without significant differences. More recently, from a small sample (14 endometriosis and 14 healthy women), Ata *et al.* (2019) observed some differences at the genus level, namely, complete absence of *Atopobium* in the vaginal and cervical microbiota and an increased presence of *Gardnerella*, *Streptococcus*, *Escherichia*, *Shigella* and *Ureaplasma* in the cervical microbiota in women with endometriosis stage 3/4. Notably, most women at this stage had *Shigella* and *Escherichia* dominant stool microbiota. From a cross-sectional study, Campos *et al.* (2018) observed higher microbial diversity in endocervical swabs and peritoneal fluid in endometriosis patients compared with the healthy group. Furthermore, dyspareunia was associated with the presence of *Ureaplasma parvum*, while *Mycoplasma genitalium* was associated with higher secretion of IFN-γ and IL-1β. Additionally, genes associated with inflammation were down-regulated in peritoneal endometriotic cells, especially in the presence of *M. genitalium*. More recently, Chadchan *et al.* (2019) described that endometriotic lesions in mice treated with broad-spectrum antibiotics were significantly smaller with fewer proliferating cells than untreated controls.

Based on this accumulated evidence, the question arises regarding how alterations of the FGT microbiota could lead to inflammatory or malignant diseases that threaten women's health. The CV sentinel immune cells would recognise different pathogen-associated molecular patterns (PAMPs), such as LPS, peptidoglycan, flagellin, glycans and damage-associated molecular patterns (DAMPs), including heat shock protein 70, calcium-modulated S100A13 and many others, by pattern recognition receptors (PRRs), including TLRs, NLRs, lectin-like receptors and others, inducing the activation and secretion of pro-inflammatory cytokines and inflammatory mediators responsible for a subclinical grades of FGT inflammation (Sheldon *et al.*, 2017). These alert signals, together with iron from both menstrual blood and ectopic endometrial tissue, are released into the peritoneal cavity, where they activate innate resident sentinel cells (i.e. macrophages, DCs and recruited neutrophils, among others) that secrete pro-inflammatory cytokines and several angiogenic growth factors, which promote the growth, implantation and neoangiogenesis of peritoneal endometriotic lesions (Laux-Biehlmann *et al.*, 2015). It is also likely that dysbiosis of the FGT microbiome and the subsequent inflammatory response may affect uterine contractility, enhancing retrograde menstruation and corresponding endometrial cell adhesion in the peritoneal compartment (Pinto *et al.*, 2015).

On the other hand, Laschke and Menger (2016) suggested a putative role for intestinal microbiota in the pathogenesis of endometriosis based on experimental evidence linking gut dysbiosis with inflammation and immune dysregulation, leading to numerous diseases. They postulated that the extent and quality of the initial immune response against episodes of retrograde menstruation could be determined by factors associated with the dysbiosis of gut microbiota, which will allow the development of endometriosis. This hypothesis was supported by the finding of Bailey and Coe (2002) on the association of endometriosis with an altered profile of the intestinal microbiota in rhesus monkeys. Moreover, there is a 50% increase in the risk of inflammatory bowel disease in women with endometriosis (Jess *et al.*, 2012). In this regard, a recent work in a murine model of peritoneal endometriosis has shown an increased gut *Firmicutes*/*Bacteroidetes* ratio, indicative of intestinal dysbiosis, 42 days after the intraperitoneal injection of endometrial tissue, together with an elevated level of *Bifidobacterium* (Yuan *et al.*, 2018). These results confirm the existence of a tight communication between the host and intestinal microbiota (Alfano *et al.*, 2018; Yuan *et al.*, 2018). Nevertheless, a cause–effect relationship between microbiota and endometriosis cannot be established because the described current evidence is still insufficient; thus, more studies are necessary to assess this theory.

On the other hand, there is emerging experimental evidence suggesting that EDC exposure can modify the vaginal (Geller *et al.*, 2018) and intestinal microbiome, leading to dysbiosis and impairment of local immune system homeostasis (Reddivari *et al.*, 2017; Rosenfeld, 2017; Malaisé *et al.*, 2018), preceding the other host alterations discussed above, such as sexual/reproductive, gastrointestinal, metabolic and hormonal disorders. Therefore, a direct multifactorial relationship can be established between genetic factors, EDCs, the microbiome and hormones, as the origin and subsequent clinical evolution of endometriosis.

Oestrogens and Microbiota

Little is known about the effect of sexual hormones on the FGT microbiome. Bezirtzoglou *et al.* (2008) revealed that *Lactobacilli* concentrations in ovariectomised rats depended on the oestradiol levels. Furthermore, it was shown that the vaginal microbiota undergoes temporal shifts in the composition and abundance of crucial species under the influence of age, sexual intercourse, hormonal variations, pharmacological treatments and hygiene habits (Shi *et al.*, 2009; Ravel *et al.*, 2011; Gajer *et al.*, 2012; Ma *et al.*, 2012; Chaban *et al.*, 2014). Hyman *et al.* (2012), using a metagenomic approach, studied the relationship between the vaginal microbiome and the levels of circulating oestradiol and progesterone in IVF-ET (*in vitro* fertilisation-embryo transfer), concluding that, although the vaginal microbiome at the embryo transfer day affects the pregnancy outcome, significant changes in the vaginal microbiota were not associated with the hormonal profiles. Nevertheless, it is well documented that the menstrual cycle is associated with changes in the vaginal microbiota. Thus, high levels of oestradiol favour a *Lactobacilli*-predominant community mainly integrated with *L. crispatus*, *L. gasseri* and/or *L. jensenii* while their relative frequency is lower under low oestrogen levels as occurs in the first phase of the menstrual cycle or in menopausal women (Gajer *et al.*, 2012). Moreover, the greater variability of vaginal microbiota is associated with menstruation. Recent work exploring the timing and fluctuations of the vaginal microbiota throughout puberty has shown

that the vaginal microbiota of perimenarcheal girls mirrors that of reproductive-age women, with a predominance of *L. crispatus*, *L. iners*, *L. gasseri* and *L. jensenii*, and, in some individuals, *Streptococcus* spp. were also detected (Hickey et al., 2015). Further studies should be carried out to increase knowledge about the link among oestrogens, vaginal glycogen levels and pH, the FGT immune system and microbiota in health and disease conditions.

On the other hand, there is increasing evidence supporting that the relationships between gut microbiota and oestrogens are directly involved in the regulation of reproductive, neurological and metabolic homeostasis, as well as in the development of several types of cancer (e.g. breast and endometrium) (Baker et al., 2017). In this regard, it has long been shown that numerous species of the gut microbiome have enzymatic activity that can metabolise oestrogens (Kwa et al., 2016). Plottel and Blaser (2011) defined the estrobolome as 'the aggregate of enteric bacterial genes whose products are capable of metabolising oestrogens'. Oestrogens are endocrine hormones synthesised in the ovaries, adrenal glands, adipose tissue and other locations, from where they are widely distributed by the bloodstream to target tissues and are metabolised and conjugated in the liver. Conjugated hepatic oestrogens can return to the bloodstream or be secreted in the intestine by the bile. Intestinal oestrogens and phytoestrogens are deconjugated from bile acids by the intestinal microbiota through the secretion of β-glucuronidases, glucosidases and hydroxysteroid dehydrogenases. Deconjugated intestinal oestrogens can be reabsorbed through the intestinal mucosa into the enterohepatic circulation and transported to distant sites, including FGT mucosal surfaces, among others. Finally, these oestrogens are eliminated by faecal and urinary excretion. Oestrogens and phytoestrogens bind to their specific oestrogen receptor alpha (ERα) and oestrogen receptor beta (ERβ) expressed in several tissues, triggering intracellular signalling pathways that result in specific physiological functions (reviewed by Wira et al., 2015). Because oestrogens induce the proliferation of epithelial cells paving the female reproductive system, sustained increased levels of these hormones have been implicated in the pathogenesis of several proliferative diseases such as endometriosis (Machado-Linde et al., 2012), endometrial cancer (Rodriguez et al., 2019) and breast cancer (Kulkoyluoglu-Cotul et al., 2019; Rižner, 2009). Dysbiosis of the gut microbiome can disrupt the estrobolome composition, resulting in higher or lower levels of peripheral blood-circulating oestrogens. Hence, exogenous estrobolome-modifying factors, including antibiotics or other drugs, EDCs, diet and other factors, may play an indirect role in the pathophysiology of FGT proliferative and inflammatory diseases causing infertility, infections, cancer and, likely, endometriosis. In this regard, endometriosis is associated with a hyper-proliferative endometrial cell state and neuroimmune communication, mainly mediated by macrophages, caused by elevated oestrogen levels (Rižner, 2009; Laschke and Menger, 2016; Liang et al., 2018).

Therefore, the consequences of high EDC exposure as a possible risk factor to develop endometriosis and promote its progression from the asymptomatic state to the different clinical stratifications of the disease may not only be a shorter AGD, which would favour frequent vulvo-vaginal faecal microbiota contamination during childhood and produce a lower grade of FGT dysbiosis, but the disease could also be mediated by alteration of the estrobolome, resulting in an anomalous level of oestrogens.

Proposed Model of Endometriosis Development

Based on epidemiological and experimental evidence, we hypothesise that there may be a direct relationship between higher prenatal exposure to oestrogens, EDCs and/or pharmaceutical compounds, a shorter AGD or other FGT alterations and a higher risk of developing endometriosis in adulthood, as shown in Fig. 3.

Therefore, a single or mixed combination exposure to EDCs (resulting in an oestrogen-like effect) throughout prenatal life could induce a shorter AGD and likely affect the physiological development of other sexual characteristics, such as the normal development of uterine endometrial tissue or the length, morphology, curvature and contractility of the uterus and fallopian tubes, which could favour neonatal and/or future episodes of retrograde menstruation after menarche and, therefore, increase the risk of developing endometriosis. Additionally, throughout childhood, a shorter AGD would favour frequent faecal microbiota contamination from the anus to the external and lower FGT (the vulva and vagina), producing an early FGT dysbiosis, which could disrupt local antimicrobial defences, mainly by increasing the vaginal pH and breaking the beneficial versus pathogenic microbial competitive balance. Interruptions of this balance would subvert the homeostasis state and generate an initial subclinical inflammatory response, which could evolve to a long-term sustained immune activation, closing the vicious circle responsible for the development of endometriosis after menarcheal age. The translocation and transport of intestinal and/or oral microbiota by the haematogenous route to FGT could also play a role in the development of endometriosis. In fact, periodontitis has been associated with endometriosis, as shown in Table IV (Kavoussi et al., 2009; Thomas et al., 2018).

Compatibility of This Hypothesis with Previous Theories

As discussed above, there is strong scientific evidence that endometriosis is a chronic inflammatory oestrogen-dependent disease mediated by an altered and sustained immune response that induces cell proliferation, along with increased cell adhesion and neo-angiogenic activity and a decreased apoptotic rate. On this basis, the mechanism proposed here, which implies a multifactorial relationship established between genetic factors, EDCs, the microbiome, the immune system and sex hormones as the origin and clinical evolution of endometriosis, is compatible with the remaining previously proposed theories. Supporting this, there is increasing evidence that EDCs dysregulate the development and function of human immune cells (Dunbar et al., 2012; Nowak et al., 2019). Additionally, some of these compounds induce alterations in human endometrial cells *in vitro*, such as an increased activation of the ERK/p38 MAPK and NFκB pathways, oxidative stress and expression of ERα (Cho et al., 2015). EDCs can also (i) affect the developmental programming of *Hox* gene expression (necessary for the development of the Müllerian system) (Block et al., 2000; Zanatta et al., 2010); (ii) alter the interactions of epithelial and stromal cells in oestrogen-dependent prenatal cells (as shown in the foetal mammary gland) (Paulose et al., 2015); and (iii) produce irreversible foetal FGT abnormalities that could be a risk factor for the development

of endometriosis in adults (Reed and Fenton, 2013). Additionally, there is increasing evidence that microbial dysbiosis can induce cellular oncogenesis by modulating host proliferative cell pathways or by interfering with the host's hormonal or immune systems (Walther-António *et al.*, 2016; Levy *et al.*, 2017; Vivarelli *et al.*, 2019). Altogether, these considerations not only support the new hypothesis but also make it compatible with previous theories.

Future Directions in Endometriosis Research

Longitudinal studies in large mother–infant cohorts should be conducted by carring out repeated measurements of serum/urine EDC levels during sensitive pregnancy windows for reproductive development and function. After childbirth, the CV microbiota and the AGD should be analysed in newborn girls, as well as during the premenarcheal stage until adulthood, carrying out a long-term follow-up on the appearance of endometriosis related to AGD and microbiota. Ongoing cohort studies in pregnant mother–girl pairs should be followed up until adulthood, looking for the appearance of endometriosis.

Detailed studies of the morphological characteristics of the upper FGT in women with and without shorter or longer AGD should also be conducted.

The potential association of FGT, intestinal and oral microbiota with the AGD and presence of endometriosis should be studied by comparisons with unaffected women, taking care to avoid including asymptomatic women with endometriosis in the reference group.

A stratification plan should be included in epidemiological studies and other investigations, considering the characteristics noted in each of the four major clinical presentations of endometriosis: superficial peritoneal endometriosis, ovarian endometriomas, deep infiltrating endometriosis (DIE) and extragenital endometriosis (e.g. lung, eye and brain).

'Keystone' microbial species associated with endometriosis should be identified.

The FGT, intestinal and oral microbiota of women with endometriosis should be studied after treatment to assess the possible association between the presence of specific microbiota characteristics and appearance of recurrences.

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Authors' roles

P.G.P. conceived the original hypothesis, wrote the manuscript, compiled and reviewed the bibliography, drew the figures and approved the final version of the article. A.J.R.A. compiled, reviewed and edited the bibliography, discussed the original hypothesis and revised and approved the manuscript. M.M.E. discussed the original hypothesis and read and approved the manuscript. P.M. discussed the original hypothesis and revised, read and approved the final version of the manuscript. F.M.L. discussed the original hypothesis and revised, read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

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