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REVIEW ARTICLE

Systematic review of cell adhesion molecules and estrogen receptor expression in the endometrium of patients with polycystic ovary syndrome

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ABSTRACT

Background: Infertility associated with polycystic ovary syndrome (PCOS) could be related to many mechanisms including endometrial factors. **Objectives:** To review cell adhesion molecule and estrogen receptor expression in the endometrium. **Search strategy:** A systematic review was performed of the Medline and Cochrane databases for papers published in any language between 2004 and 2014. The search term was “polycystic ovary syndrome’ OR ‘Stein Leventhal syndrome’ OR ‘anovulation’ AND ‘endometrium’ OR ‘endometria.’” **Selection criteria:** Research studies on endometrial cell adhesion molecules and estrogen receptor expression among women with PCOS diagnosed according to the Rotterdam criteria were included. **Data collection and analysis:** Data were extracted from identified studies and the quality of assessment was analyzed. **Main results:** Six studies were included. Data were controversial with respect to MUC1 and $\alpha V\beta 3$ integrin expression with significantly higher and lower levels, respectively, in women with PCOS. Estrogen receptor expression was enhanced among patients with PCOS as compared with healthy women. **Conclusions:** Endometrial factors influence embryo receptivity as indicated by the molecular mediators identified in the studies, including cell adhesion molecules and the estrogen receptor.

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1. Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder among women during their reproductive life, affecting 5%–7% of the population [1]. It is a frequent cause of infertility, anovulatory menstrual disorders, and hirsutism [2]. A consensus workshop in Rotterdam in 2003 indicated that PCOS is confirmed if a patient meets any two of three criteria: oligoovulation and/or anovulation, excess androgen activity, and polycystic ovaries (as assessed by gynecologic ultrasonography) [3].

After an extensive review of the literature, Prapas et al. [4] reported that several genetic factors are involved in this complex syndrome. In fact, they found a wide range of changes in genes related to various signaling pathways, such as sexual hormone action, gonadotropin mechanism, insulin activity, homeostasis, and persistent inflammation status. These alterations show that PCOS is a complex disease with numerous variables. Irrespective of the exact mechanisms underlying

PCOS, infertility and endometrial changes are the real challenges for specialists and investigators.

Recent studies on gene expression in endometrial tissue [2–5] have shown that some genes that are present in the proliferative phase of the menstrual cycle could be related to DNA replication and thus lead to cell proliferation and remodeling. These endometrial changes are related to the estrogen receptor [5–10]. After ovulation, when the progesterone level is high, the endometrium undergoes a series of changes including blocking of tissue growth, DNA synthesis, and mitosis, which together mark the beginning of cellular differentiation and prepare the endometrium for possible embryonic implantation. Blocking of the growth of epithelium could be related to progesterone-regulated gene expression, including downregulation of the estrogen receptor and upregulation of enzymes involved in the metabolism of estrogen by 17 β -hydroxysteroid dehydrogenase—processes that effectively minimize the action of estradiol in epithelial cells [5]. A disturbance in progesterone and estrogen action could therefore affect endometrial physiology, possibly influencing the maternal–fetal interaction and penetration of the embryo [5].

Progesterone action after ovulation promotes decidualization of the endometrial stromal cells, which is marked by transformation of the cytoskeleton, including downregulation of the actin of smooth muscle and upregulation of prolactin, insulin-like growth factors

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(IGFs), IGF-binding proteins, insulin receptor, and relaxin. This process is essential to control embryo invasion and to establish a proper environment of cytokines and immunomodulators in the stroma during invasion. Other substances are also important in embryo interaction, such as cell adhesion molecules [6,7].

Cell adhesion molecules are found on the surface of the cell, and mediate cell–cell adhesion and contact between the cell and the extracellular matrix. According to structural and functional similarities, they are divided into five groups: cadherins, mucins, selectins, integrins, and the immunoglobulin superfamily [6]. These substances could participate both in the maternal–fetal interaction mechanism and in the endometrial proliferation process.

Women with PCOS are known to have a higher risk of hyperplasia and endometrial malignant neoplasm, in addition to implantation problems. Evidence suggests that abnormal gene expression and clinical manifestations—e.g. improper deployment of the embryo, spontaneous abortion, and endometrial malignant neoplasm—might be related to the chronicity of the disease, the absence of opposition to estrogen action on the endometrium, hyperinsulinemia, hyperandrogenism, and the effects of growth factors such as IGF [7]. The end result of these events could influence endometrial physiology and cell adhesion molecules. The estrogen receptor could also affect cell adhesion molecules [8].

There are few studies documenting the changes in endometrial factors in PCOS. As a result, the aim of the present review was to evaluate endometrial features of PCOS, particularly cell adhesion molecules and estrogen receptor expression.

2. Materials and methods

In a systematic review, the Medline and Cochrane databases were searched for reports published in any language between January 1, 2004, and February 28, 2014, with the search term “‘polycystic ovary syndrome’ OR ‘Stein–Leventhal syndrome’ OR ‘anovulation’ AND ‘endometrium’ OR ‘endometria.’” References cited in the research articles extracted from the databases were also evaluated. Human studies, those assessing cell adhesion molecules and estrogen receptor expression in the endometrium of women with PCOS, and those in which the Rotterdam criteria [3] were used to diagnose PCOS were eligible for inclusion. Review studies and animal models conducted exclusively for experimentation or cell cultures were excluded. Systematic reviews and meta-analyses were consulted, but only data from the original articles were included in the review.

Data were extracted from identified articles. Quality assessment was performed independently by two reviewers (M.C.P.B. and R.S.S.). If there was disagreement, a third reviewer (J.M.S.-Jr.) was consulted. The analysis followed the PRISMA statement for systematic reviews.

3. Results

A total of 467 articles were identified (Fig. 1). Careful reading of the titles and summaries, and application of the inclusion and exclusion criteria led to the exclusion of 461 manuscripts. Only cross-sectional, observational, phase 2 studies were included; no phase 3 studies were eligible.

Table 1 shows the results of studies on cell adhesion molecules in the endometrium of women with PCOS. Integrin expression levels were lower among patients with PCOS than among control women in two studies [9,10], but no differences were found in a third study [11]. Expression of MUC1 was higher among women with ovulatory PCOS than among control women in one report [12], but showed no changes in another study [10].

Assessment by immunohistochemistry and immunoblotting using monoclonal antibodies to MECA-79 and HECA-452 (two L-selectin ligands) in one study [13] showed that patients with PCOS exhibited significantly lower MECA-79 and HECA-452 staining than did fertile women.

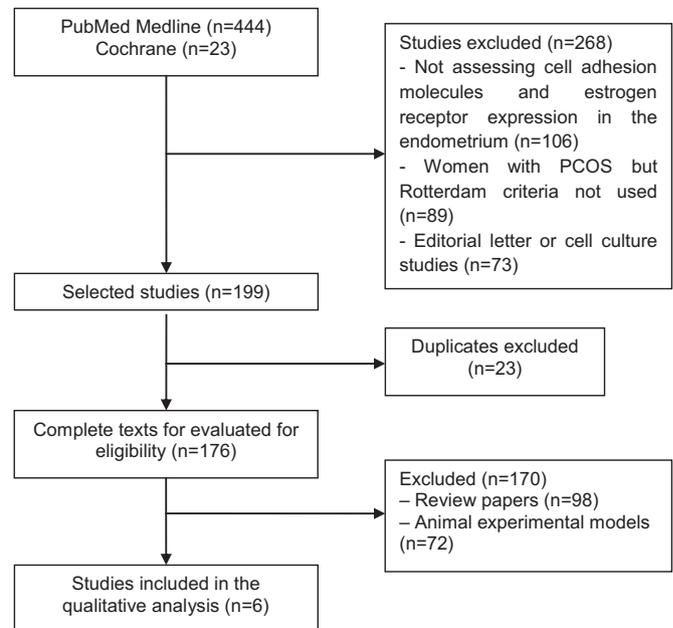


Fig. 1. Flowchart of study selection. Abbreviation: PCOS, polycystic ovary syndrome.

Table 2 shows the results of estrogen receptor expression in the endometrium of women with PCOS. One study [10] reported higher expression of the estrogen receptor among patients with PCOS during the midsecretory phase. Another [14] described higher levels of the estrogen receptor and increased androgen receptor expression during the proliferative phase.

4. Discussion

The studies selected for the present review show that alterations occur in molecular cell adhesion during the secretory phase or during progesterone treatment among women with PCOS. However, there were not enough data to propose a hypothesis. Not only was the number of cases small, but there were limitations to data comparisons. However, hyperexpression of the estrogen receptor was more consistent across studies and might influence endometrial physiology and molecular cell adhesion [5,7,9].

Integrins, a type of cell adhesion molecule belonging to the transmembrane glycoprotein family, are formed by the noncovalent binding of the α and β subunits. They are associated with many physiological processes—e.g. those favoring embryo development, hemostasis, formation of a thrombus, scar remodeling, defense mechanisms (immune and non-immune process), and carcinogenesis—and are considered markers of endometrial receptivity [15]. Although most integrins are constitutively expressed throughout the menstrual cycle, a few exhibit a regulated expression pattern, such as $\alpha 1\beta 1$, $\alpha 4\beta 1$, and $\alpha V\beta 3$ [16]. These integrins are possibly reduced in infertile women or in women with irregular menstrual patterns [16].

Furthermore, aberrant expression patterns of the $\alpha V\beta 3$ integrin have been connected with infertility and other gynecologic disorders such as endometriosis, secretory phase deficiency, and PCOS [9–13]. Expression of the $\alpha V\beta 3$ integrin and its osteopontin ligand coincides with the beginning of the implantation window, which is triggered by the upregulation of adhesion ligands associated with the reduced expression of inhibitory elements that could represent potential barriers to implantation [17]. The *HOX* genes, a subgroup of homeobox genes, are recognized as essential for proliferation, differentiation, and endometrial receptivity processes because they regulate specific molecular markers related to the implantation window (e.g., the $\beta 3$ integrin subunit) [17].

Table 1

Studies included in the assessment related to adhesion molecules.

Author, year of publication	Study type	Number of patients	Ages	Endometrial biopsy (day of cycle)	Results
Lopes et al., 2014 [9]	Cross-sectional	40 with PCOS 40 with normal cycles	18–40 y	Midsecretory phase (days 20–24)	Women with PCOS exhibited reduced expression levels of integrin and intercellular adhesion molecules
Margarit et al., 2010 [12]	Cross-sectional	26 with ovulatory PCOS 15 with anovulatory PCOS 33 with normal cycles 25 with endometriosis	18–40 y	Midsecretory phase (days 6–8 after LH surge)	Women with ovulatory PCOS presented significantly higher levels of MUC1 than did those with anovulatory PCOS or normal cycles
Margarit et al., 2009 [13]	Cross-sectional	26 with PCOS 33 fertile women 25 with endometriosis 33 with unexplained infertility	Fertile women: 28.4 ± 4.76 y Women with PCOS: 28.9 ± 3.02 y	Midsecretory phase (days 20–22)	Women with PCOS or endometriosis exhibited significantly lower MECA-79 and HECA-452 staining than did fertile women
DuQuesnay et al., 2009 [11]	Cross-sectional	10 with PCOS 31 with normal cycles 9 fertile women	Fertile women: 35.2 y Women with PCOS: 33.1 y	Midsecretory phase (days 20–22)	No difference in integrin expression levels
Quezada et al., 2006 [10]	Cross-sectional	8 with PCOS 8 with normal cycles	Women with normal cycles: 33.9 ± 1.3 y Women with PCOS: 29.5 ± 5.4 y	Midsecretory phase (days 19–23)	Women with PCOS exhibited reduced integrin levels No difference in MUC1 expression levels

Abbreviations: PCOS, polycystic ovary syndrome; LH, luteinizing hormone.

Quezada et al. [10], using immunohistochemistry in a cross-sectional study to analyze the endometrium of women with PCOS, found an important decrease in integrin expression as compared with a control group. Lopes et al. [9] detected the reduced expression of not only integrin but also intercellular adhesion molecules during the secretory phase among women with PCOS [9]. By contrast, in another evaluation of the endometrium of PCOS women, DuQuesnay et al. [11] found no significant differences [11]. Investigators have not yet reached a consensus on integrin levels in the endometrium of women with PCOS.

Mucins are characterized by their long, filamentous structure and high proportion of glycans. They are expressed abundantly in many epithelia, primarily luminal tissues such as the gastrointestinal tract and the reproductive system. Members of the mucin family are high-molecular-weight glycoproteins and, among the cloned human mucins, only MUC1 and MUC6 have been found in the human endometrium [18]. MUC1 is a transmembrane protein expressed on the epithelial cell surface of the cervix, endometrium, and uterine tube. Its functions include cellular lubrication, epithelial protection, and anti-adhesion activity. In vitro experimental studies of the human endometrium have shown that MUC1 expression increases during the implantation window, but decreases with embryo implantation, perhaps owing to blastocyst-derived factors [19]. Horne et al. [20] raised the hypothesis of an association between MUC1 expression and infertility. They found that the increase in MUC1 expression was associated with implantation failure among women with primary infertility treated by in vitro fertilization.

Within the scope of PCOS, an immunohistochemical study [12] identified lower expression of MUC1 in the endometrium of fertile women or women with anovulatory PCOS as compared with infertile women with PCOS. However, another study evaluating the endometrium of women with PCOS and those with regular menses [10] found no difference in MUC1 expression between the two groups. The increase in the

former study was thought to be related not only to MUC1 expression but also to estrogen action. The low number of cases and the type of controls in many studies, particularly in the immunohistochemical study [12], prevent us from drawing any conclusions. As a result, further studies are necessary to investigate the role of MUC1 in the endothelium among women with PCOS.

In a study of selectin expression in the endometrium, Margarit et al. [13] analyzed ligand expression via MECA-79 and HECA-452 monoclonal antibodies. They observed that MECA-79 expression among fertile women increased most between the proliferative and the secretory phase of the endometrium, and that MECA-79 epitopes were expressed at a lower level among infertile women with PCOS than among fertile women, suggesting that high-affinity interactions between L-selectins and their ligands have a role in embryo invasion [13]. Lopes et al. [9] reported similar results; however, the low dose of oral progesterone with which their patients were treated most probably interfered with the outcome.

Evidence indicates that, irrespective of the endometrial phase, the estrogen receptor is more highly expressed among women with PCOS [10,14]. Some of the studies that were analyzed [10,14] reported an increase in expression of estrogen receptor- α (ER- α) in the stroma without identifying, however, any changes in expression in the epithelium. By contrast, in a study of women with PCOS and those with normal menstrual cycles, Gregory et al. [21] found higher ER- α expression both in the stroma and in the epithelium among women with PCOS. Their study was not included in the present review, however, because it was published before the 2003 Rotterdam consensus.

Although the data on high estrogen expression are consistent, those on cell adhesion molecules are conflicting [9–13]. The studies are hindered by a low number of patients, the wide spread of clinical findings on PCOS, the possible influence of obesity on the factors investigated,

Table 2

Studies included in the assessment related to estrogen receptor.

Author, year of publication	Study type	Number of patients	Ages	Endometrial biopsy (day of cycle)	Results
Quezada et al., 2006 [10]	Cross-sectional	8 patients with PCOS 8 with normal cycles	Women with normal cycles: 33.9 ± 1.3 y Women with PCOS: 29.5 ± 5.4 y	Midsecretory phase (days 19–23)	Women with PCOS exhibited increased ER- α expression levels
Villavicencio et al., 2006 [14]	Cross-sectional	34 patients with PCOS 17 with normal cycles 10 with endometrial hyperplasia	Women with normal cycles: 36.9 ± 1.58 y, Women with PCOS: 26.3 ± 0.88 y	Proliferative phase	Women with PCOS exhibited increased ER- α and AR expression levels

Abbreviations: PCOS, polycystic ovary syndrome; ER, estrogen receptor; AR, androgen receptor.

heterogeneity of the control groups, insulin resistance and metabolic disturbances that potentially interfere with the results, and the women's ages. As a result, further studies conducted with a large number of both lean and obese women with PCOS in comparison to control women of similar weight and with regular menses both before and after progesterone treatment or ovulation induction are necessary to analyze molecular cell adhesion in the endometrium.

Polycystic ovary syndrome is a complex disorder with reproductive, endocrine, and metabolic consequences. Women with this syndrome are infertile not only because of anovulation, but also, in all likelihood, because of endometrial abnormalities that are possibly connected with molecular mediators including cell adhesion molecules, cytokines, growth factors, and lipids, which could be biochemical markers of endometrial receptivity. There is both consistent and conflicting evidence for these associations. Thus, additional research is needed to further understand the influence of cell adhesion molecules on endometrial receptivity and, consequently, the poor reproductive performance of women with PCOS.

Conflict of interest

The authors have no conflicts of interest.

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