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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 αVβ3 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.

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 metabolization of estrogen by 17β-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.

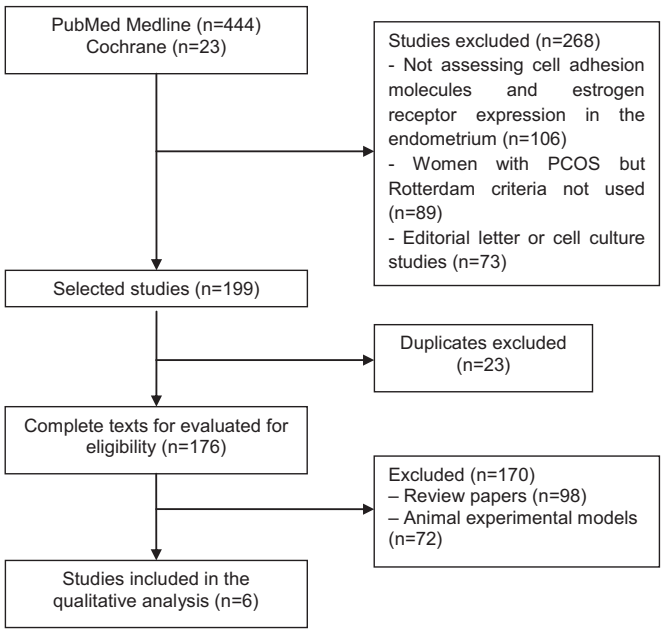

Fig. 1. Flowchart of study selection. Abbreviation: PCOS, polycystic ovary syndrome.

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 α1β1, α4β1, and αVβ3 [16]. These integrins are possibly reduced in infertile women or in women with irregular menstrual patterns [16].

Furthermore, aberrant expression patterns of the αVβ3 integrin have been connected with infertility and other gynecologic disorders such as endometriosis, secretory phase deficiency, and PCOS [9–13]. Expression of the αVβ3 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 β3 integrin subunit) [17].